DISSERTATION TITLED

"QTc DISPERSION IN CARDIAC AUTONOMIC NEUROPATHY AND ITS CORRELATION WITH DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES - THE BASIS FOR NON ISCHEMIC DIABETIC CARDIOMYOPATHY"

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CERTIFICATE

This is to certify that the dissertation **"QTc DISPERSION IN CARDIAC AUTONOMIC NEUROPATHY AND ITS CORRELATION WITH DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES - THE BASIS FOR NON ISCHEMIC DIABETIC CARDIOMYOPATHY"** is a bonafide work done by **Dr. SUBASHINI.V** Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, during March 2016 to August 2016 in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2014 – 2017.

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ABBREVATIONS

ADA	-	American Diabetic Association
ANOVA	-	Analysis of variance
BMI	-	Body mass index
CAN	-	Cardiac autonomic neuropathy
CAD	-	Coronary Artery Disease
CRP	-	C – Reactive Protein
CV	-	Cardio Vascular
DM	-	Diabetes mellitus
DM	-	Diabetes Mellitus
DN	-	Diabetic Nephropathy
DNA	-	Deoxyribonucleic acid
DD	-	Diastolic Dysfunction
GCT	-	Glucose Challenge Test
GDM	-	Gestational Diabetes Mellitus
HbA1c	-	GlycatedHaemoglobin.
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
LV	-	Left ventricle
QTD	-	QT Dispersion

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INTRODUCTION

INTRODUCTION

Cardiac Autonomic neuropathy common and worst complication of diabetes mellitus. Diabetic cardiac autonomic neuropathy (CAN), major complication seen in one-sixth of insulin dependent type 1 diabetes and one-third of non insulin dependent diabetic patients, related with increased morbidity.

CAN is related with poor prognosis and may lead to postural hypotension, exertional intolerance, enhanced intraoperative instability, increased silent myocardial infarction ischemia and left ventricular (LV) dysfunction.

Diabetics with cardiac autonomic neuropathy are prone for sudden cardiac death due to silent myocardial ischemia or due to ventricular arrhythmias.CAN increases with obesity, age, poor glycemic control, and may be with duration of diabetes

The association between CAN and QT interval prolongation demonstrated in more studies and it predispose to sudden cardiac death in diabetes. Increased QT dispersion(QTD) is suggested as marker of diabetic cardiac autonomic neuropathy.

In one study Sacre et al. estimated the association of CAN with LV dysfunction. This author found patients with CAN had systolic and diastolic dysfunction at rest, and systolic dysfunction after exercise. They found association between diastolic function and CAN, not dependent on metabolic factors and other factors contributing to LV dysfunction. The relative dominance of sympathetic activity at onset of CAN will stimulate renin-angio tensin aldosteronesystem(RAAS), which increases hemodynamic stresses and energy requirements of left ventricle by sodium retention and peripheral vasoconstriction. It may exert direct noxious effects on cardiomyocytes (apoptosis of cardiomyocytes and regression to fetal phenotype) changes in nature of extracellular matrix(ECM) by stimulation of myocardial fibrosis, which further alter architecture and impair performance of left ventricle.

Such sympathetic overactivity, in association with regional myocardial autonomic denervation present in more advanced stage of CAN, have been recently shown that may lead to decreased coronary blood flow capacity and diastolic dysfunction in a insulin independent diabetic patients with features of early micro vascular changes. The confirmation of presence of CAN in a otherwise healthy type 2 diabetes patients, and its independent relation with resting diastolic dysfunction(DD), is important. Most of the research data regarding QT

interval and diabetic CAN are found in type 1 diabetes with only very few studies in type 2 diabetes. This study is aimed to find out the association of corrected QT (QTc) interval and QTc dispersion with diabetic cardiac autonomic neuropathy in type 2 diabetes attending diebetic op or medical op at ggh so that we can found the subset of diabetic patients who are at risk for sudden death and to find correlation between CAN and diastolic dysfunction-the basis for non ischemic diabetic cardiomyopathy.

Several treatment options including graded exercise, cardioactive drugs, and intensive medication for contolling many risk factors of CAN which are joined with treatment for macrovascular complication that have been shown to improve functional deficiency in autonomic nervous system(ANS). Therefore, noninvasive detection of early stages of CAN using QT dispersion and 2D echo may necessitates the need for definite control of cv risk factors, so by decreasing risk of early mortality.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

- To study the utility of prolongation of corrected QT interval in the ECG to diagnose CAN in patients with diabetes mellitus and to study the prevalence of diastolic dysfunction-the basis for non ischemic cardiomyopathy?
- To study the prevalence and risk factors for cardiac autonomic neuropathy

REVIEW OF LITERATURE

REVIEW OF LITERATURE

VARIOUS DESCRIPTION OF DIABETES MELLITUS (DM)

EGYPTIAN DESCRIPTION

Historical clinical description of Diabetes Mellitus found in the Ebers Papyrus, 18th Egyptian Dynasty of about 1500 BC.

Ebers papyrus : early clinical description of diabetes (Egyptian, 1500 BC)

INDIAN DESCRIPTION

In India described as “Sweetness of urine” .

GREEKS DESCRIPTION

3rd century Greeks only first used term diabetes 1100 years later.

Aretaeus of Cappadocia in Asia Minor, in the 1st century AD given the first description .He is the first physician to describe diabetes formally. He explained it as " passing of copious amounts of urine and the loss of body flesh"

Willis in 1674 who described "sweetness of the urine" and found that it was secondary to sweetness in the blood. 100 years later it was identified that sweetness may due to increased level of sugar, and 50 years later this was found as " glucose"

In 1890 von Mering and Minkowski identified pancreatic factor after identification of glycosuria following pancreatectomy in dogs. In 19th century it was thought that diabetes may be multifactorial not a single disease. Bernard identified the biochemical details of diabetes as the production of glucose by the liver .Association of coma with acidosis also found during this period .

In 1922 Ideas of Banting, with technical help of Best, facilities and support of MacLeo and biochemical expertise of Collip produce adequately pure and more potent preparation of bovine insulin . Following which long acting preparations of insulin came into market after decades by Hagedorn and Hallas-Moller, .

TECHNICAL MILESTONES IN THE MANAGEMENT OF DIABETES

Year	Worker(s)	Milestone
1797	Rollo	Dietary management
1913	Alien	Severe calorie restriction
1921	Banting, Best, Collip, Macleod	Isolation and use of insulin
1936	Hagedorn and colleagues	Protamine-insulin complexes used
1939	Loubatieres	Discovery of Sulphonylureas
1970	Jorgensen and Colleagues	Highly purified insulin available
1976	Sonksen and colleagues Walford and Colleagues	Self blood glucose monitoring
1976	Koenig and colleagues	Glycosylated haemoglobin to Monitor control
1979	Goeddel and colleagues	Genetically engineered insulin
1980	Many researchers	Microcomputers in diabetes management

DEFINITION

Diabetes occurs because of "the presence/absence of factors that act against insulin or lack of insulin". Due to insufficient insulin action resulting in increase in blood sugar level (hyperglycaemia) .Patient develop diabetic acidosis due to accumulation of ketone bodies resulting in morbidity

DIAGNOSIS

It is diagnosed by blood glucose level done in accredited lab

WHO criteria for the diagnosis of diabetes

1 Symptoms of diabetes plus casual venous *plasma* glucose ≥ 11·1 mmol/l. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss

2 Fasting *plasma* glucose ≥ 7·0 mmol/l or whole blood ≥ 6·1 mmol/l. Fasting is defined as no calorie intake for at least 8 hours

3 2 hour *plasma* glucose ≥ 11·1 mmol/l during oral glucose tolerance test using 75 g glucose load

In the absence of symptoms, these criteria should be confirmed by repeat testing on a different day. If the fasting or random values are not diagnostic, the 2 hour value post-glucose load should be used

Note:
Fasting plasma glucose < 6·1 mmol/l—normal
Fasting plasma glucose ≥ 6·1 and < 7·0 mmol/l—impaired fasting blood glucose
Fasting plasma glucose ≥ 7·0 mmol/l—provisional diagnosis of diabetes; the diagnosis must be confirmed (see above)

Adapted from *Diabetes Care* 1997;20:1183-1195

CLASSIFICATION OF DIABETES MELLITUS

Diabetes is divided into four main groups as type 1, type 2, other specific types, and Gestational diabetes. Type 1 diabetes because of absolute lack of insulin results from pancreatic islet cell destruction mostly an autoimmune process. They tend to develop ketoacidosis and require insulin therapy. Type 2 diabetes the most common type of diabetes, is a heterogeneous disorder most commonly associated with insulin resistance mechanisms with relative insulin deficiency due to abnormalities of insulin secretion .

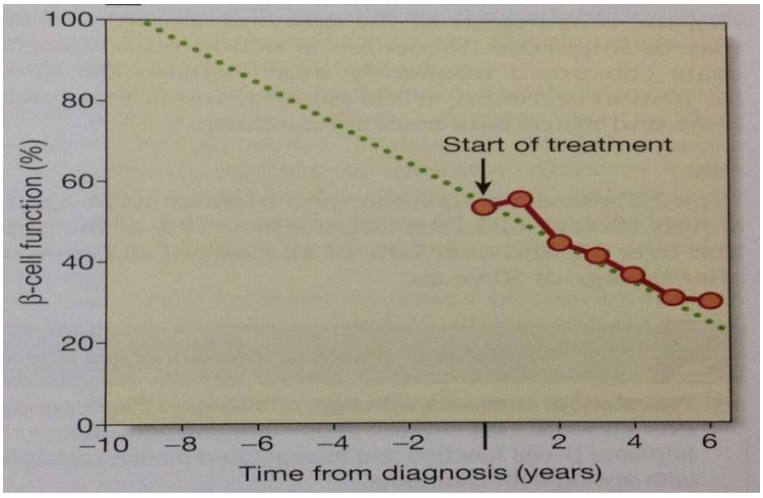
Comparison of Type 1 and Type 2 diabetes

Type 1 diabetes	Type 2 diabetes
Inflammatory reaction in islets	No insulitis
Islet B-cells destroyed	B-cells function
Islet cell antibodies	No islet cell antibodies
HLA related	Not HLA related
Not directly inherited	Strong genetic basis (some cases)

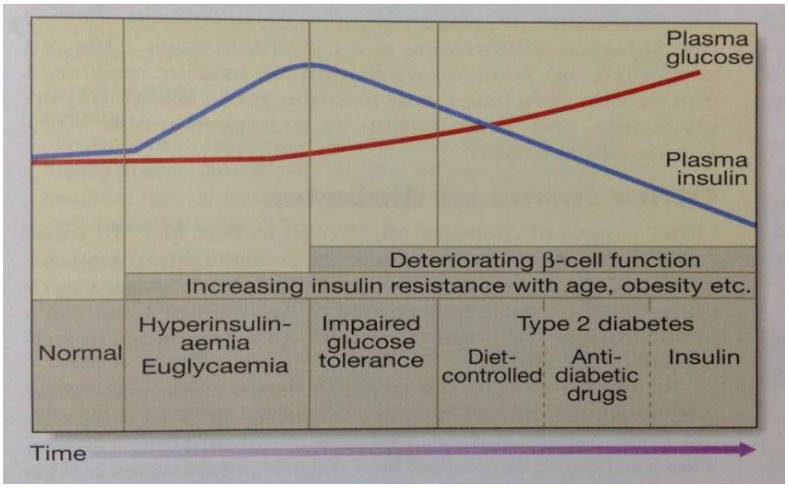
TYPE 1 DIABETES MELLITUS

Results from an autoimmune attack triggered by many factors such as environmental and genetic in a susceptible individual . It begins very early in life .

TYPE 2 DIABETES MELLITUS



TYPE 2 DM NATURAL HISTORY



Other specific types of diabetes

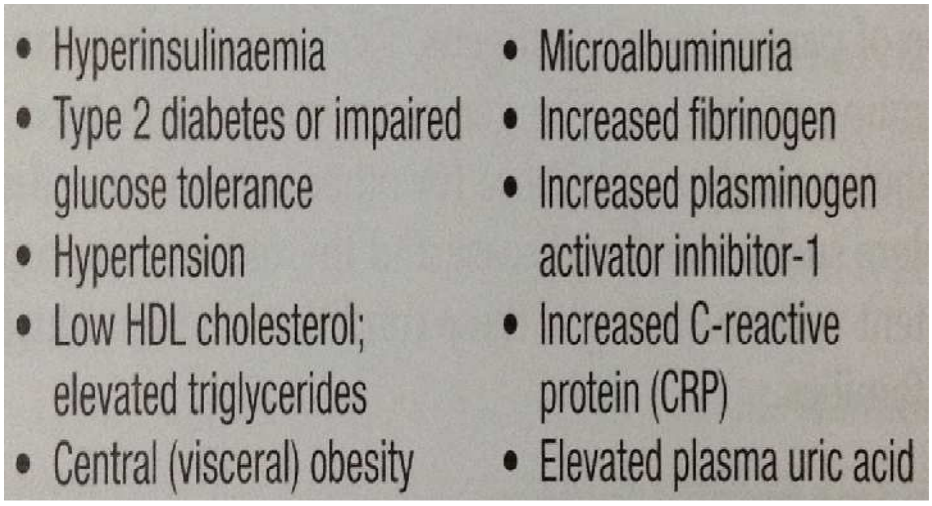
- *Genetic defects of β cell function*—chromosome 12 hepatic nuclear factor-1α (HNF-1α) (formerly maturity onset diabetes of the young (MODY) 3), chromosome 7 glucokinase defect (formerly MODY 2), chromosome 20 HNF-4α (formerly MODY 1), mitochondrial DNA mutation
- *Genetic defects in insulin action*—Type A insulin resistance (genetic defects in insulin receptor), lipoatrophic diabetes, genetic defects in the PPARγ receptor
- *Gestational diabetes*
- *Diseases of the exocrine pancreas*—pancreatitis, pancreatectomy, carcinoma of pancreas, cystic fibrosis, fibro-calculous pancreatopathy, haemochromatosis
- *Endocrinopathies*—acromegaly, Cushing's disease, Conn's syndrome, glucagonoma, phaeochromocytoma, somatostatinoma
- *Drug induced* (these agents in particular exacerbate hyperglycaemia in patients with established diabetes)—corticosteroids, diazoxide, β adrenergic agonists (for example, intravenous salbutamol), thiazides, α interferon
- *Uncommon forms of immune mediated diabetes*—stiff man syndrome, anti-insulin receptor antibodies (Type B insulin resistance)
- *Infections*—congenital rubella, cytomegalovirus
- *Other genetic syndromes sometimes associated with diabetes*—Wolfram syndrome, Down's syndrome, Turner's syndrome, Klinefelter's syndrome, Prader-Willi syndrome

PATHOGENESIS OF TYPE 2 DM

There are numerous causes for type 2 DM . The underlying mechanism is either due to diminished insulin secretion— an islet cell defect, associated with increased peripheral resistance to action of insulin .It results in decreased peripheral glucose uptake, or increased hepatic glucose output. Probably as many as 98% of Type 2 diabetic patients are "idiopathic"—that is, no specific causative defect has been identified.

It is a slowly progressive disease . Some individual above twenty years of age who presented insulin independent diabetes

become insulin dependent It is known as " latent autoimmune diabetes of adulthood " (LADA) They have autoantibodies against insulin.

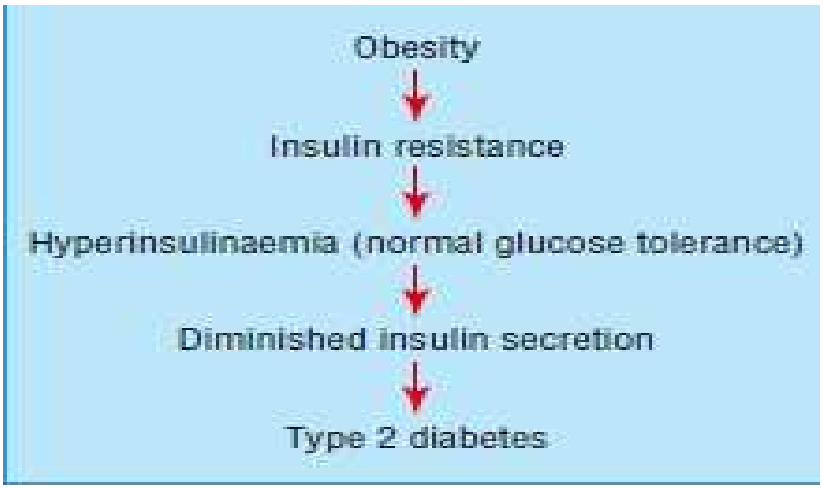


RISK FACTORS FOR TYPE 2DM

Increased risk for Type 2 diabetes

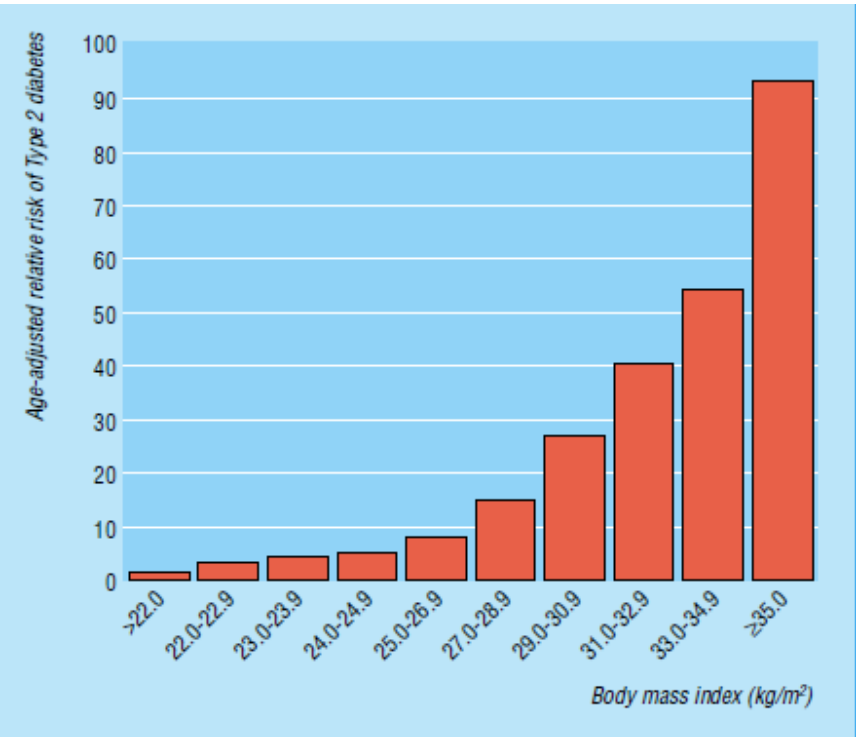
- People over 40 years of age
- People of Asian or African-Caribbean ethnic origin
- Overweight people
- Family history of diabetes
- History of gestational diabetes
- History of large baby (birth weight exceeding 4 kg)

OBESITY



Natural history of Diabetes Mellitus

Fat distribution is related to development of diabetes mellitus. Waist hip ratio is .8 in males and .9 in females are more akin to development of this diseases. Many studies showed the correlation . use of leptin as a marker for this studies It is under trial



TYPE 2 DM IN CHILDREN AND YOUNG ADULTS

It is recently estimated that 8% and 45 % are found to be type 2 DM in U.S. diagnosed at the age of 12 -14 years .Most of the children are girls associated with obesity and positive family history .

MITOCHONDRIAL DIABETES

Rare form of type 2 DM seen in young and thin individuals associated with microvascular complications . They do better with sulphonyureas . It is related to A3243G DNA mutation .

INSULIN RESISTANCE DIABETES

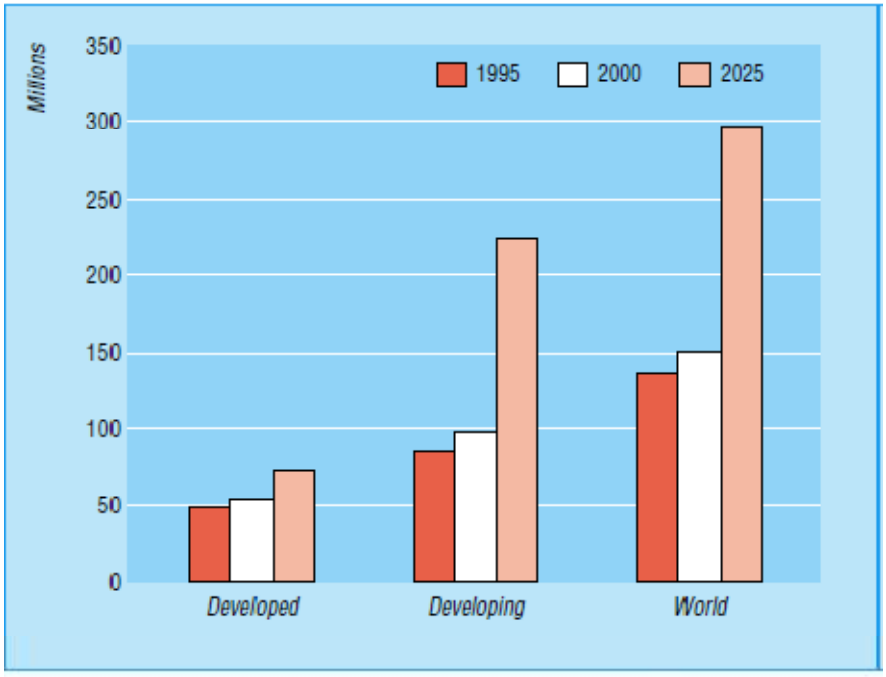
They often associated with acanthosis nigricans ,lipodystrophy and dyslipidemia. Type A due to receptor defect . IgG autoantibodies against insulin receptor is seen in type b diabetes

PREVALENCE

Worldwide, incidence of Type 2 diabetes is rising very rapidly: , it was estimated that about 140 million people are diabetics in the year of 1996 . This estmates doubles in another 30 years mainly in developin and under developed countries

GEOGRAPHICAL VARIATIONS

More prevalent in Asian and African- carribean and in some inner urban areas .Asian people have higher incidence of diabetic nephropathy (DN) and coronary artery disease (CAD) .



Number of people aged ≥ 20 years estimated to have Type 2 diabetes in developed and developing countries

DIABETIC COMPLICATIONS

Diabetes affect almost every organ in the body . It is divided into micro and macro vascular complications .

PATTERN OF PRESENTATION

Type 2 diabetes—presentations

• Diabetic symptoms	53%
• Incidental	29%
• Infections (for example, candida)	16%
• Diabetic complications	2%

Identifying patients in need of insulin

Symptoms
- Rapid onset
- Substantial weight loss
- Weakness
- Vomiting

Signs
- Usually thin
- Dry tongue
- Weak

Ketoacidosis
- Drowsiness
- Dehydration
- Overbreathing
- Breath smelling of acetone

Age
- Any, more likely under 30 years

Blood glucose concentration
- Any

Other indications
- When tablets have failed during pregnancy
- When diet has failed during intercurrent illness
- In patients who have undergone pancreatomy

- Ill patients need admission
- Others may start insulin at home
- If there is any doubt use insulin

AIMS OF TREATMENT

HEALTHY LIFESTYLE

"Diabetes is easy to diagnose, but can be managed with negligent ease by those inclined to do so" **RB Tattersall, 1990**

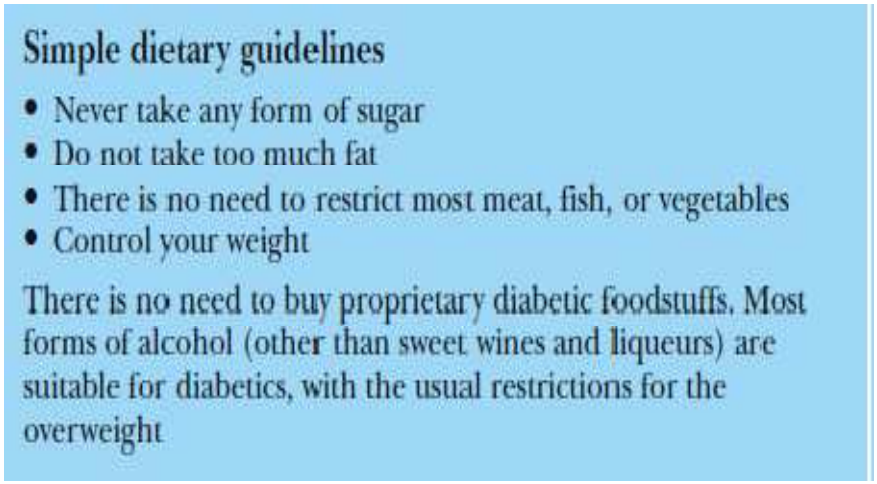
Treatment aims

- Save life
- Alleviate symptoms
- Prevent long-term complications
- Reduce risk factors:
  - smoking
  - hypertension
  - obesity
  - hyperlipidaemia
- Educate patients and encourage self-management
- Achieve goals of St Vincent declaration (see page 82)

Targets for control of diabetes

	Very good*	Acceptable	Less than ideal
Body mass index (kg/m^2)	<25	<27	>27
HbA_{1c} (%) (normal 4.0-6.0)	<6·5	6·5-7·5	>7·5 (>8·0 poor)
Blood glucose in Type 2 diabetes† (mmol/l):			
Fasting	<5·5	<8.0	≥10.0
Postprandial	<9·0	<10·0	≥10·0

*This is the ideal and may be difficult, impossible, or unnecessary to achieve in certain patients (for example, elderly people)
Individual targets should be established for each patient
†The optimal range in Type 1 diabetes is about 4·0-9·0 mmol/l



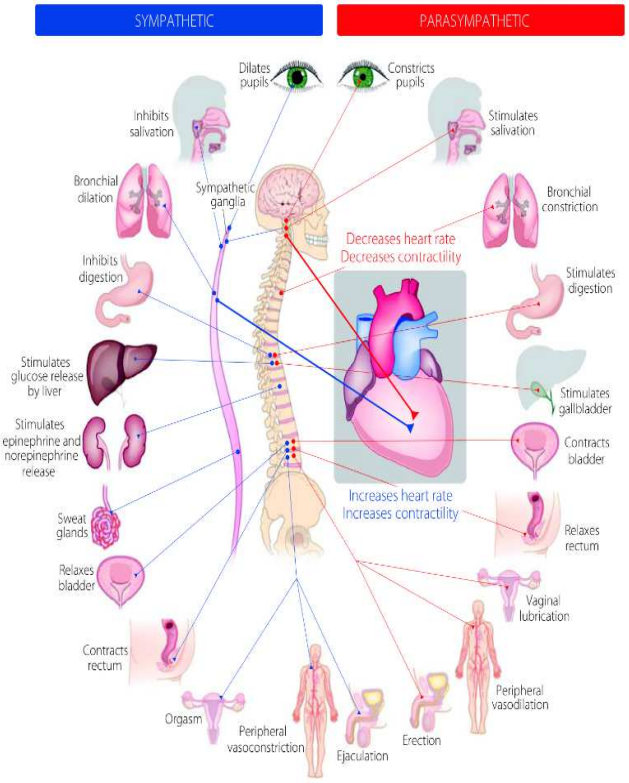
AUTONOMIC NERVOUS SYSTEM (ANS)

The autonomic nervous system send sensory impulses from all of the organs through nerves to brain such as medulla, pons and hypothalamus. They do not reach our consciousness, but elicit automatic or reflex responses through efferent autonomic nerves, eliciting appropriate reflexes of the heart, vascular system and all organs of body to variations in surrounding temperature, lying supine or standing postures, food intake, other changes to which all the individuals are exposed. Two components of ANS are sympathetic and parasympathetic system .

FUNCTION OF AUTONOMIC NERVOUS SYSTEM

Function of ANS is regulation of internal organs . when there is ANS dysfunction ,function of maintaining homeostasis and adapting to stress is not effective .

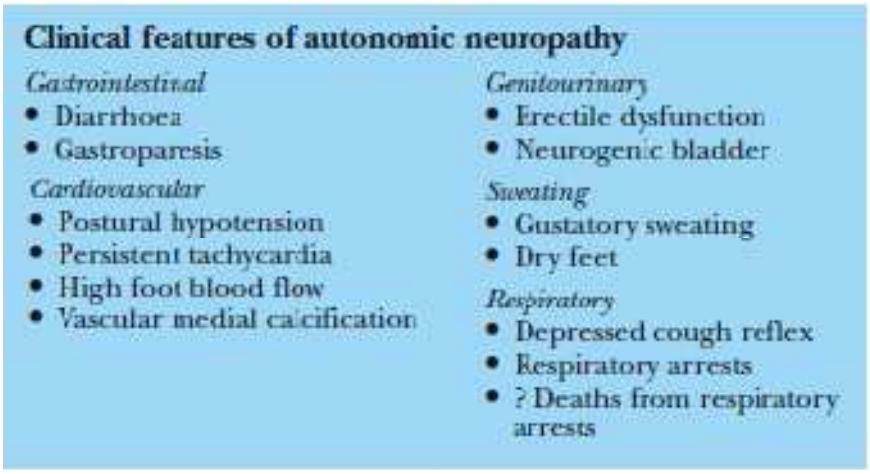
FUNCTION OF ANS



AUTONOMIC DYSFUNCTION

Autonomic dysfunction is part of acute or chronic peripheral neuropathies (e.g: Diabetic, alcoholic-nutritional, Amyloidosis, Gullain-Barre syndrome, infections, heavy metal toxic and porphyrias).

CLINICAL FEATURES OF AUTONOMIC DYSFUNCTION

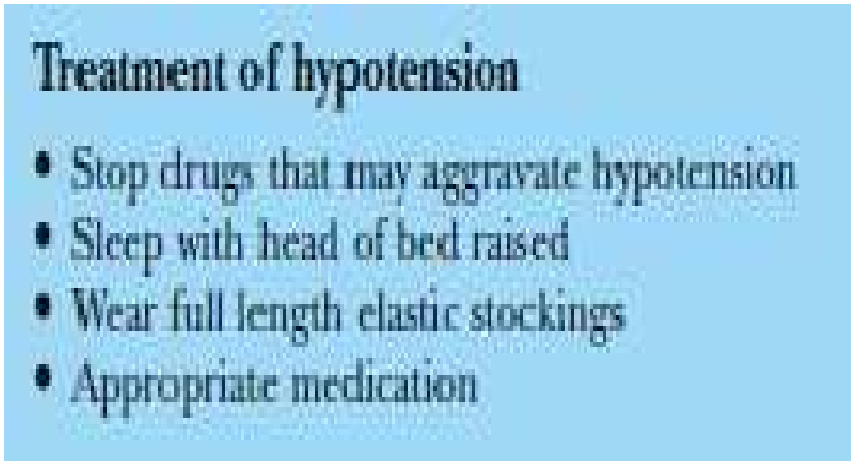


CARDIOVASCULAR SYSTEM

POSTURAL HYPOTENSION

Systolic blood pressure fall more than 20mmHg on standing for three minutes is defined as postural hypotension. Symptoms developed when fall is more than 30mmHg .

TREATMENT OF HYPOTENSION



GUSTATORY SWEATING

Gustatory sweating. The sweating is highlighted by strarch – iodide powder

While eating tasty food is an early sign of autonomic neuropathy.

DIAGNOSIS OF CAN

Bedside tests for CVS are used to exclude autonomic neuropathy. Cardiac autonomic function test are done using cans analyser which is shown in the figure.

Normal values for autonomic function tests*

	Normal	Abnormal
Heart rate variation (deep breathing) (beats/min)	> 15	< 10
Increase in heart rate on standing (at 15 seconds) (beats/min)	> 15	< 12
Heart rate on standing 30: 15 ratio	> 1·04	< 1·00
Valsalva ratio	> 1·21	< 1·20
Postural systolic pressure fall at 2 min	< 10 mm Hg	> 30 mm Hg

*These test results decline with age. The figures apply generally in those less than 60 years old.

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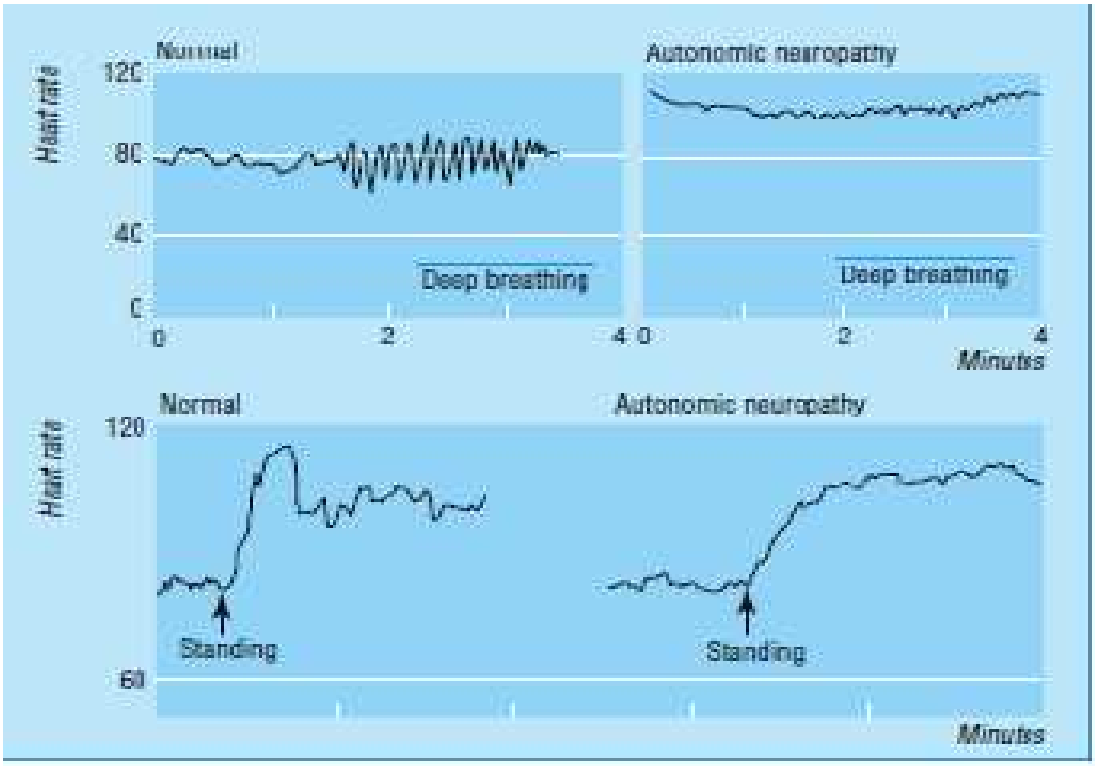


Heart rate changes in a normal subject (left) and a patient with autonomic neuropathy (right) showing loss of heart rate variation in autonomic neuropathy during deep breathing, at six breaths a minute (top), and loss of "overshoot" cardiac acceleration on standing (bottom).

CANS ANALYSER

CLINICAL TESTING OF AUTONOMIC NEUROPATHY

Test (in following order)	Position	Approximate time of test (min)	Apparatus required
Heart-rate response to Valsalva manoeuvre	Sitting	5	Aneroid manometer, electrocardiograph
Heart-rate variation during deep breathing	Sitting	2	Electrocardiograph
Blood-pressure response to sustained handgrip	Sitting	5	Handgrip dynamometer, sphygmomanometer
Immediate heart-rate response to standing	Lying to standing	3	Electrocardiograph
Blood-pressure response to standing			Sphygmomanometer

First rule out end organ damage before subjecting the patient to CAN tests. It is valid, significant time tested procedures to diagnose autonomic neuropathy noninvasively more specific. Co-morbid illness, usage of drugs like anti-histamines, antidepressants, anti-tussives, aspirin should not be there. Patients instructed to

abstain from smoking and drinking coffee at least one hour before the test.

Heart rate response to deep breathing

Heart rate changes with respiration . This is determined by parasympathetic system. To evaluate this response, patient is instructed to lie down quietly and is asked to take slow deep breaths at a rate of six per minute. ECG monitors maximum and minimum heart rate.

Heart rate response to standing

Patient is asked to get up from supine position and heart rate to this response is calculated. After standing, the heart rate normally increases and is maximum at about fifteenth beat after attaining erectl posture. The heart rate then starts falling and is minimum at about thirtieth beat. Hence R-R variation between fifteen and thirtieth beats are monitored.

Valsalva maneuver

Originally used as a method to expel pus from middle ear which is done by blowing and straining with closed nose and mouth.

The patient first takes a deep breath and then expires forcibly against a closed glottis for a period of ten to twenty seconds.

Alternatively to test for autonomic function, patient needs to blow into a sphygmomanometer such that a pressure level of at least forty mms is maintained for thirty seconds. Valsalva maneuver is associated with a short duration increase of intraocular pressure as well as intra cranial pressure. This leads to a risk of hemorrhage within the eye and dislocation of lens. The risk is somehow known to be low because similar increase in pressure occur in day to day activities also.

There are four phases explained as normal response to valsalva maneuver.

Phase 1: at the beginning of straining, there is a short duration of increase in intrathoracic pressure which causes increased BP and decreased heart rate. This happens because the elevated pressure compresses the aorta thereby propelling blood into peripheral circulation.

Phase 2: This is the straining phase where there is decrease in BP initially which later is recovered. There is associated reflex

tachycardia, stroke volume reduces because of decrease in venous return.

Phase 3: cessation of straining in this phase causes an increase in venous return. There is an abrupt but transient fall in BP and increased heart rate.

Phase 4: this is the overshoot phase where the event returns to pre-valsalva state after about 6 to 8 beats. There is an initial overshoot of BP wide pulse pressure and also reflex bradycardia. ECG tracing during the maneuver are taken to calculate ratio between longest and shortest R-R interval. Normal is 1.6.

Systolic blood pressure response to standing

Otherwise known as postural hypotension and has been discussed earlier.

Diastolic BP response to sustained handgrip

A hand grip dynamometer is used to detect increase of systolic and diastolic BP and chang in heart rate. The patient is supposed to squeeze the dynamometer to its maximum followed by a slow release to keep it at a level of at least 30 % of maximum for 120 to 180 seconds. Normally after the hand grip is released, there will be an

increase of diastolic BP to more than 16 mm of Hg. Abnormal response is less than 10 mm of Hg increase in BP.

We look for reduced variability (less of a change in heart rate), a sign that the patient's heart response, as provided by the body's autonomic control center, is not adequate. At least two tests must be performed in order for the test to be conclusive. Sometimes one test result may be abnormal, but the second test result turns out normal.

This is because some heart rate variability tests are more sensitive to earlier autonomic nervous system dysfunction than others. This is also due to the fact that test results are based on a combination of activities within the body, which are influenced differently in each patient. As a general rule, the more tests that result in abnormal results, the more severe the end organ damage is to the autonomic nervous system.

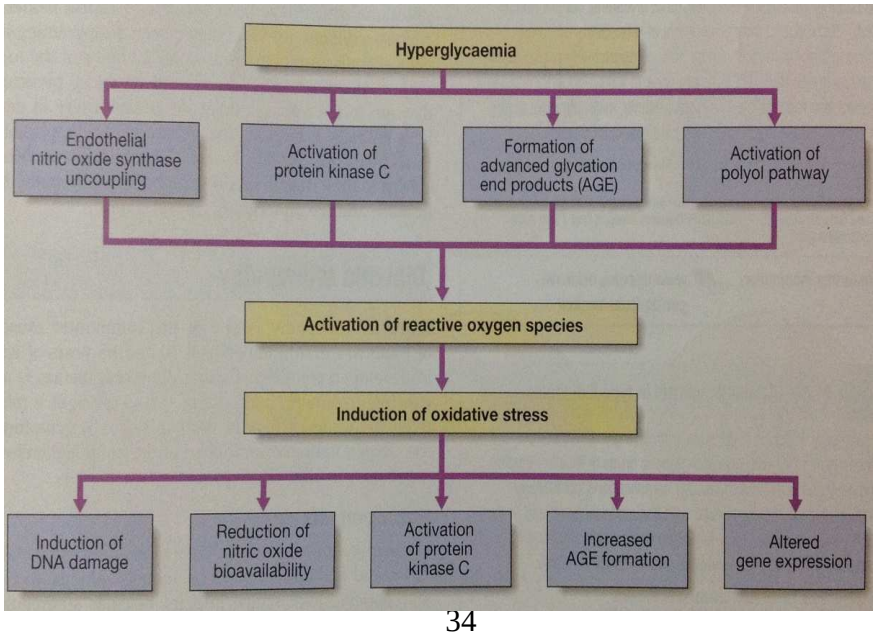
Perhaps the most important things we can do for our patients with diabetes are to make them aware of autonomic neuropathy, to let them know whether they have it, and to help them keep blood sugar levels in an acceptable range.

Doing so not only helps reduce the risk of heart disease, but also lowers the risk of diabetic eye, kidney and nerve disease, each of which patients want to avoid.

Diabetic autonomic neuropathy has been called a "silent killer," because so few patients realize that they suffer from it, and yet its effects can be so lethal. With a brief, 15-minute test that we can administer in the office, and some relatively modest interventions, we can help many patients live longer, healthier lives.

PATHOGENESIS OF DAN:

Autonomic dysfunction that accompanies diabetic neuropathy is the one that has extensively evaluated.Several different factors have been implicated in this pathogenic process.



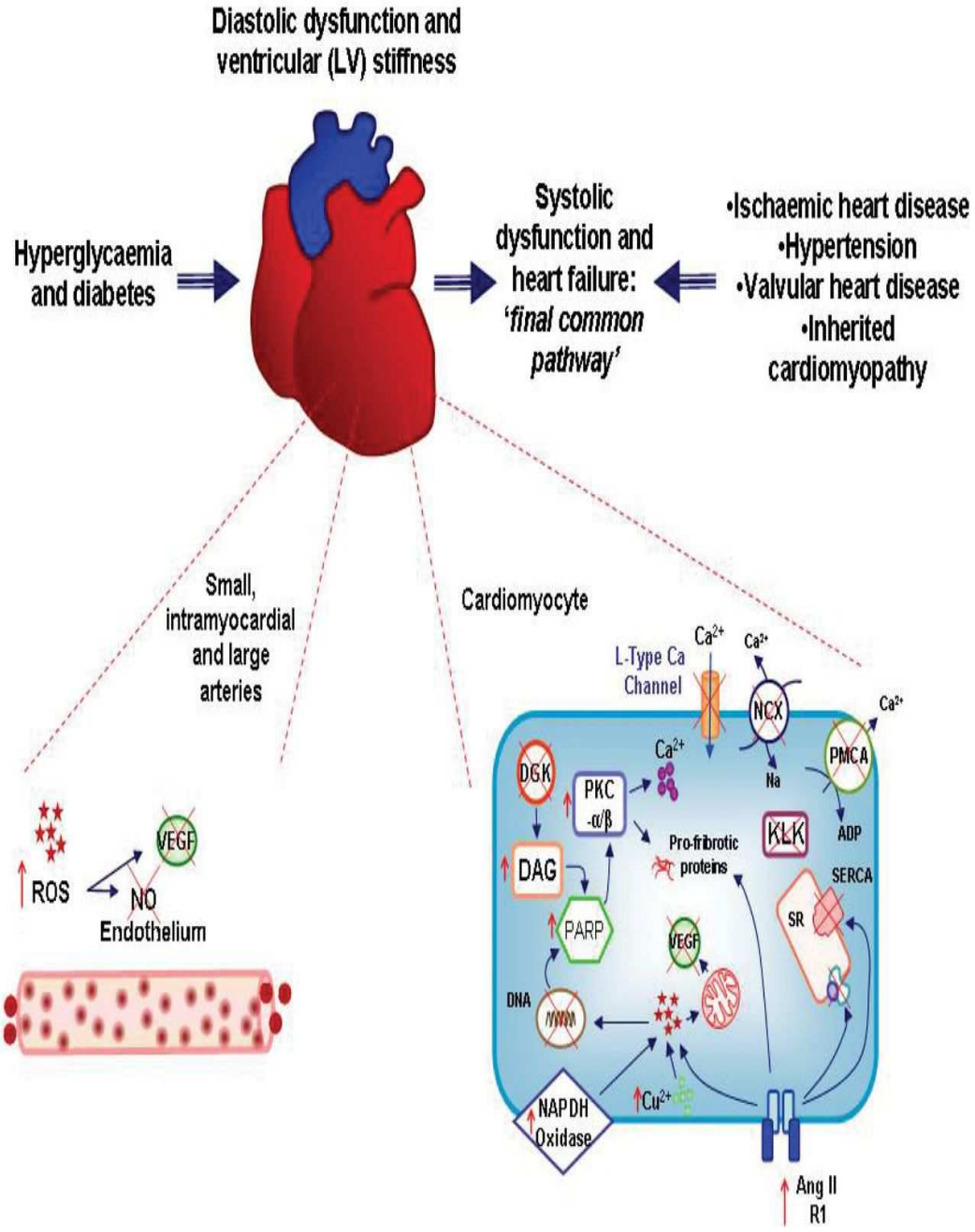
DIABETIC CARDIOMYOPATHY

Cardiovascular morbitidy and mortality accounts for 65% in diabetic patients . Hence ADA accepted it as coronary equivalents. It affects heart in three ways .1)atherosclerosis related CAD 2) Cardiac autonomic neuropathy 3) Diabetic cardiomyopathy (DbCM) . Third entity is poorly understood by Physicians and Diabetologists .

Rubler et al first described DbCM as “Myocardial dysfunction in the absence of valvular heart diseases coronary heart diseases and hypertension”. Heart failure is common complication in diabetic patients . It affect the quality of life . Hence it is of utmost importance in early identification of this Condition .

EPIDEMIOLOGY

In many trials its prevalence is estimated as 19 -26% but actual prevalence of DbCM is not fully estimated. Prevalence of diastolic dysfunction in one study around 30% In other studies it is still more high.Various criteria for selection and imaging techniques may explain this disparity .


Diastolic dysfunction and ventricular (LV) stiffness
Hyperglycaemia and diabetes
Systolic dysfunction and heart failure: 'final common pathway'
•Ischaemic heart disease
•Hypertension
•Valvular heart disease
•Inherited cardiomyopathy
Small, intramyocardial and large arteries
ROS
VEGF
NO
Endothelium
Cardiomyocyte
L-Type Ca Channel
Ca2+
NCX
Na
PMCA
ADP
DGK
PKC -α/β
DAG
Pro-fribrotic proteins
KLK
SERCA
SR
PARP
VEGF
DNA
NAPDH Oxidase
Cu2+
Ang II R1

PATHOGENESIS AND PATHOPHYSIOLOGY

It is not fully defined yet .It is multifactorial .Various proposed mechanisms include 1) metabolic 2) insulin resistance 3) cardiac autonomic dysfunction and myocardial fibrosis 4) alterations in RAAS .

METABOLIC MECHANISM

HYPERGLYCEMIA AND HEART

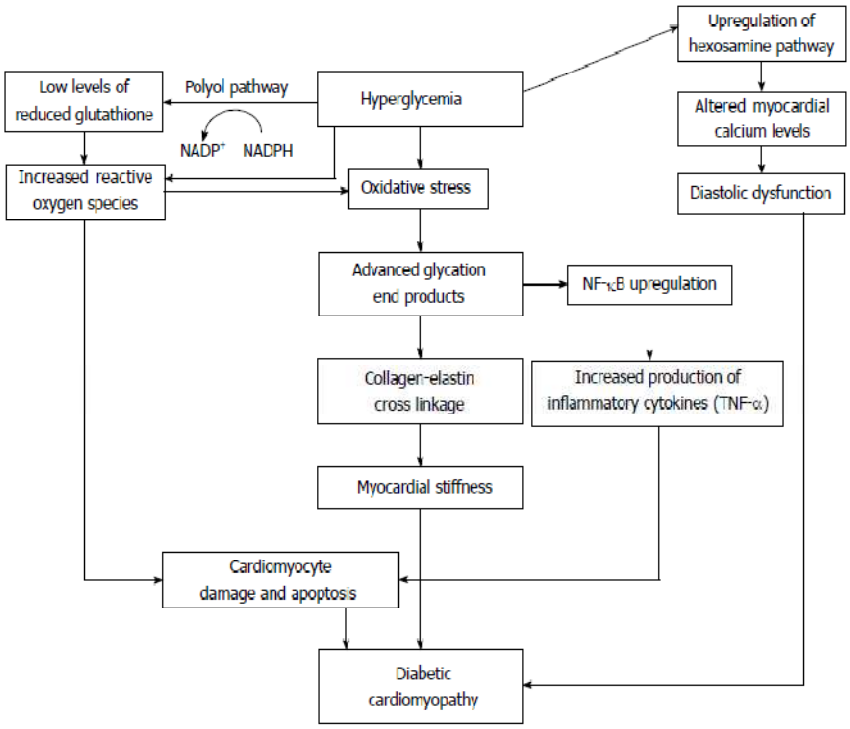


Figure 1 Mechanism of myocardial damage resulting from hyperglycemia. NADPH: nicotinic acid adenine dinucleotide phosphate; NF-κB: Nuclear factor-κB; TNF-α: Tumour necrosis factor-α.

LIPID METOBOLISM AND HEART

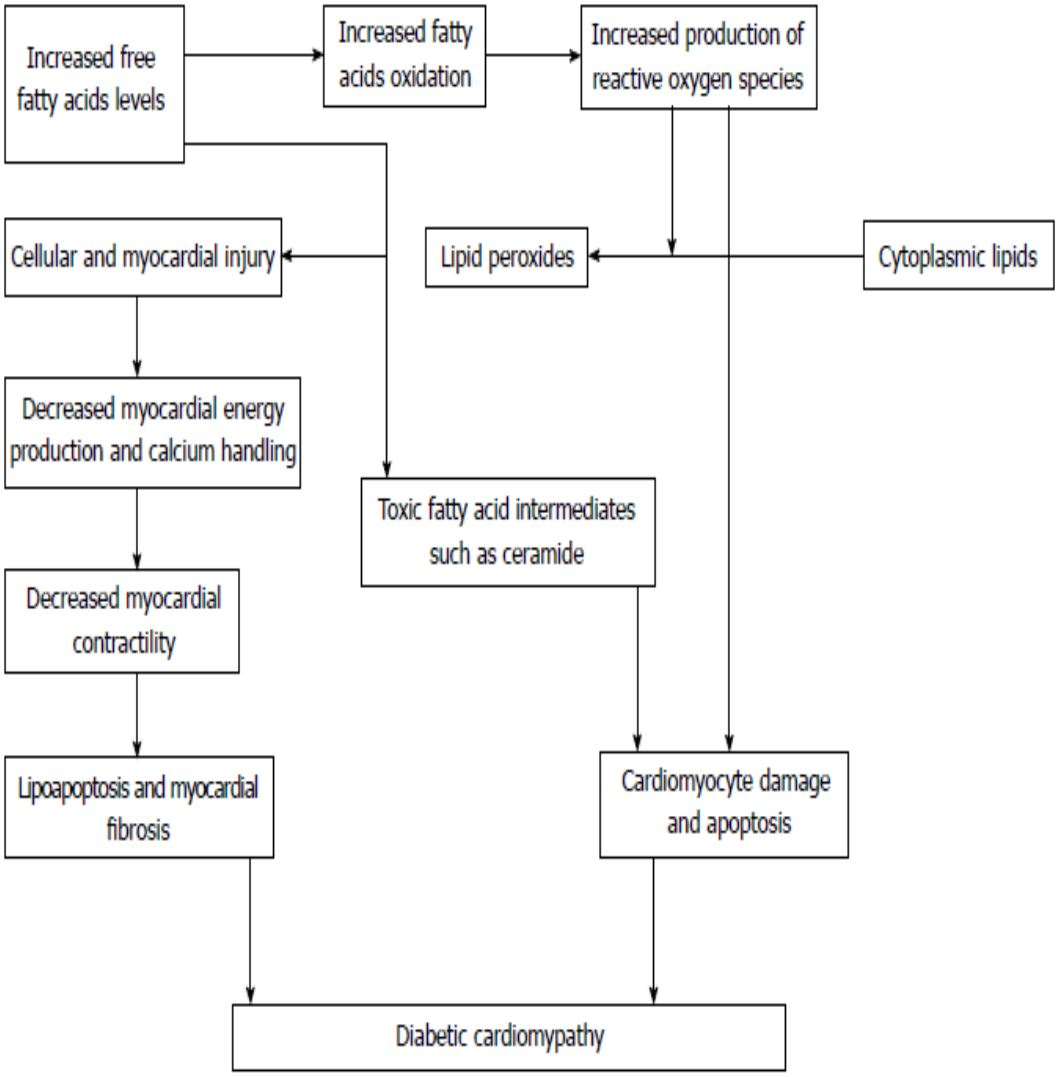


Figure 2 lipotoxic cardiac injury in diabetic cardiomyopathy.

Cardiac steatosis is recently proposed mechanism for DbCM.

ROLE OF HYPERINSULINEMIA AND INSULIN RESISTANCE

Cardiac myocyte hypertrophy results due to hyperinsulinemia. BNP is a marker of cadiac myocyte hypertrophy .Genetic alterations occurs as of it leading to activation of transcriptional factors and to hypertrophy and deposition of ECM cause focal fibrosis in heart of diabetic patients .

CONTRIBUTION FROM MICROVASCULAR ISCHEMIA

Ischemia leads to myocardial rigidity, scaring andcardiac dysfunction in DbCM . Microvascular complications of diabetes are diabetic retinopathy and neuropathy. In diabetes ischemia resulting from microvascular disease affects vasa vasorum further damages medium arterioles and small arterioles of the diabetic heart .

ROLE OF RAAS

High blood glucose stimulates intra-cardiac RAS.It show various effects on myocardial cells. Intracellular AGT □ levels are found to be 3-4fold higher in cardiac muscle cell of diabetic patients when compared to normal individual.

CAN AND DbCM

Because of abnormalities in heart rate and vascular hemodynamics DbCM is a common complication . It is seen in longer duration of diabetes .Its prevalence is higher in diabetes . Patients with cardiac autonomic neuropathy are found to have decrease in vascular elasticity and increase in peripheral vascular resistance due to abnormal sympathetic tone. Reduction of myocardial perfusion reserve was shown by few investigators. This will partly explain ventricular dysfunction related with diabetic CAN.

Diabetes causes structural change functional alterations in cardiomyopathy. It is divided into three stages .They are early ,middle and late stage. Cardiac changes at molecular level will be seen in early stage there will be diastolic dysfunction and hypertrophy of ventricles .ejection fraction is normal.

Middle stage is a continuously progressive disease .Myocardial fibrosis occurs and progressing ventricular hypertrophy results. Systolic dysfunction starts to occur along with diastolic dysfunction. In late stage it deteriorates further.

Diagnostic evaluation of DbCM

Diabetic cardiomyopathy in early stage will have subclinical features in the form of cardiomyocyte damage .It is detected by strain or tissue Doppler. Later stage can be diagnosed by our routine 2D echo .

ECHOCARDIOGRAPHY

Echocardiography is a cost effective simple diagnostic tool .It identifies structural and fuctional changes of heart .Usually ventricular diastolic function is assessed by blood flow across mitral valve using pulse Doppler.

During echo E/A is measured . It is the ratio between early ventricular filling /late ventricular filling Based on ratio it is graded as normal I/II/III . But it has low sensitivity and specificity

We can use tissue dopper for regional motion abnormality Newer technics have come into field MIBG MRI can be done to assess diastolic dysfunction.

STAGES	CHARACTERISTICS	FUNCTIONAL FEATURES	STRUCTURAL FEATURES	METHODS
Early stage	Depletion of GLUT4 Increased FFA Carnitine deficiency Ca2 homeostasis changes Insulin resistance	No overt functional abnormalities or possible overt diastolic dysfunction but normal ejection fraction	Normal LV size, wall thickness, and mass	Sensitive methods such as strain, strain rate, and myocardial tissue velocity
Middle stage	Apoptosis and necrosis Increased AT II Reduced IGF-I Increased TGF-1 Mild CAN	Abnormal diastolic dysfunction and normal or slightly decreased ejection fraction	Slightly increased LV mass, wall thickness, or size	Conventional echocardiography or sensitive methods such as strain, strain rate, and myocardial tissue velocity
Late stage	Microvascular changes Hypertension CAD Severe CAN	Abnormal diastolic dysfunction and ejection fraction	Significantly increased LV size, wall thickness, and mass	Conventional echocardiography

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DURATION

This study was done over a period of six months.

STUDY POPULATION

The study comprised of type 2 Diabetes Mellitus patients visiting the Outpatient(OP) department of institute of diabetology,or medical OP institute of internal medicine, Rajiv Gandhi Government General Hospital(RGGGH)and Madras Medical College, Chennai. Age and sex matched healthy volunteers served as controls.

Sample Size

Total Number of Subjects	:	200
Number of controls	:	100
Number of Type 2 Diabetes Mellitus cases	:	100

TYPE OF STUDY

Observational study

ETHICS COMMITTEE APPROVAL:

Obtained.

INCLUSION CRITERIA

1.Patients of type 2 diabetes

Exclusion Criteria

1.Ischaemic Heart Disease/structural heart diseases

2.Patients on pacemakers

3.Chronic obstructive pulmonary disease

4.Secondary Diabetes Mellitus

5.Anti-hypertensive and Anti-arrhythmic drugs

6.Dyselectrolytemia

7.Hyperthyroidism or hypothyroidism

8.Type1 Diabetes

9.Gestational diabetes

DATA COLLECTION AND METHODS

METHODOLOGY

Data collected from all those who fulfilled the inclusion and exclusion criteria after taking a detailed case history and obtaining a written informed consent.

METHOD OF COLLECTION OF DATA

Baseline data including age and sex, detailed medical history including conventional risks factors, clinical examinations and

relevant investigations are included as part of the methodology. For all the subjects standing height and weight were measured. Hundred patients of type 2 diabetes mellitus of more than five years duration and 100 age and sex matched controls without any history of diabetes were selected .Cardiac autonomic function tests will be done in all cases and controls.Cases and controls were undergone Echocardiography .Cases with diastolic dysfunction were subjected to cardiac stress testing to exclude ischemic disease. QTc dispersion were measured and compared with diastolic dysfunction among patients with and without autonomic neuropathy and controls

Product / Procedure / Investigation Details

1.12 lead simultaneous electrocardiograms (ECG).

2. Manual measurement of QT interval and RR interval; and QTD

will be calculated using Bazets formula

3.Cardiovascular Autonomic Function tests with CANS analyzer

4. 2DEchocardiography

5. Cardiac stress testing (If applicable)

INTERPRETATION OF THE TEST WAS BASED ON THE WORKS OF EWING AND CLARKE[16]

Score	Heart rate variability test			Blood pressure test	
	Deep breathing	**Valsalva Ratio**	**Response to standing**	**Response to handgrip**	**Response to standing**
0	>15	>1.20	>15	>15	≤ 10
1	11-15	1.11-1.20	12-15	11-15	11-29
2	≤ 10	≤1.10	<12	≤ 10	>30

For grading of cardiovascular autonomic function, results are classified into normal, mild and severel (scores 0,1,2 respectively). An overall score of '0' or '1' was considered normal, score 2,3,4 were considered mild and score ≥5 were judged was severel autonomic function[56].

QT interval was taken from the onset of QRS complex to the end of T wave. QT was then corrected for heart rate using the Bazette's formule[44].

QTc interval = QT / √(R – R). A QTc interval more than 440 Millisecond is considered prolonged.

All the data will be entered in proforma(enclosed).The statistical software using SPSS version 20.0 was used for the analysis of data and MS word and Excel have been used to generate graphs, tables etc.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

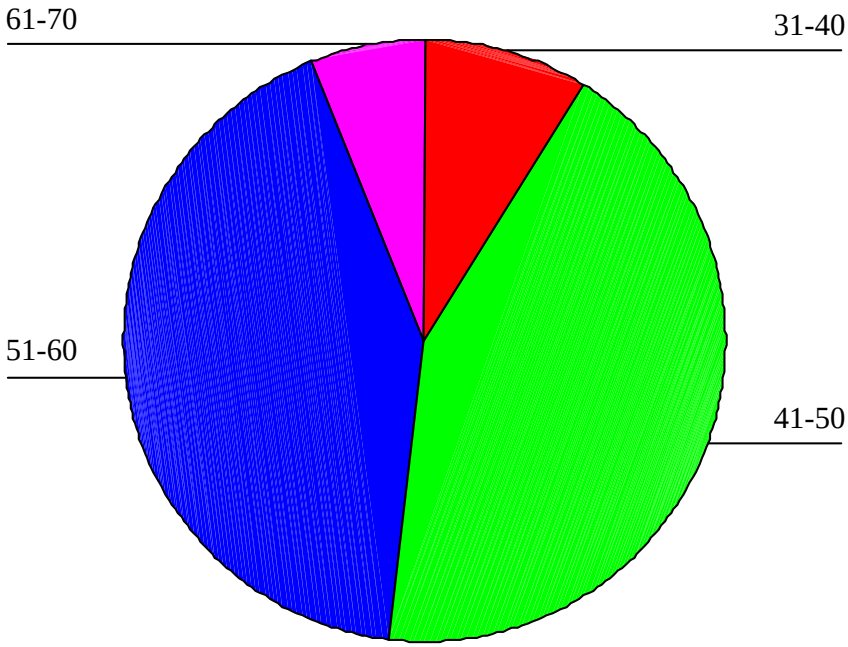
The present study was done to evaluate the prevalence of cardiac autonomic neuropathy in type 2 diabetes mellitus . 100 cases of type 2 diabetic cases were considered for this study and 100 age and sex matched healthy individuals were chosen as controls. The mean age of control and cases are presented in table 1A. A sex wise distribution of control and study groups are shown in table 1B.

AGE DISTRIBUTION

Age Group in years (CASES)

Age Group in years	n	%
31-40	9	9.0
41-50	43	43.0
51-60	42	42.0
61-70	6	6.0
Total	100	100.0

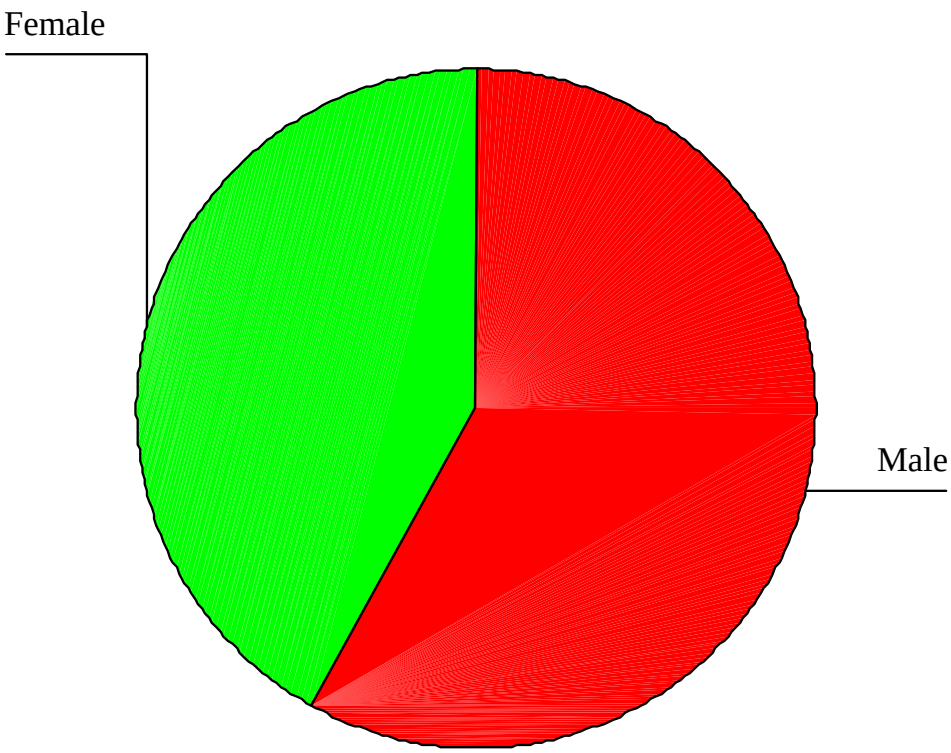
Age Group in years



SEX DISTRIBUTION

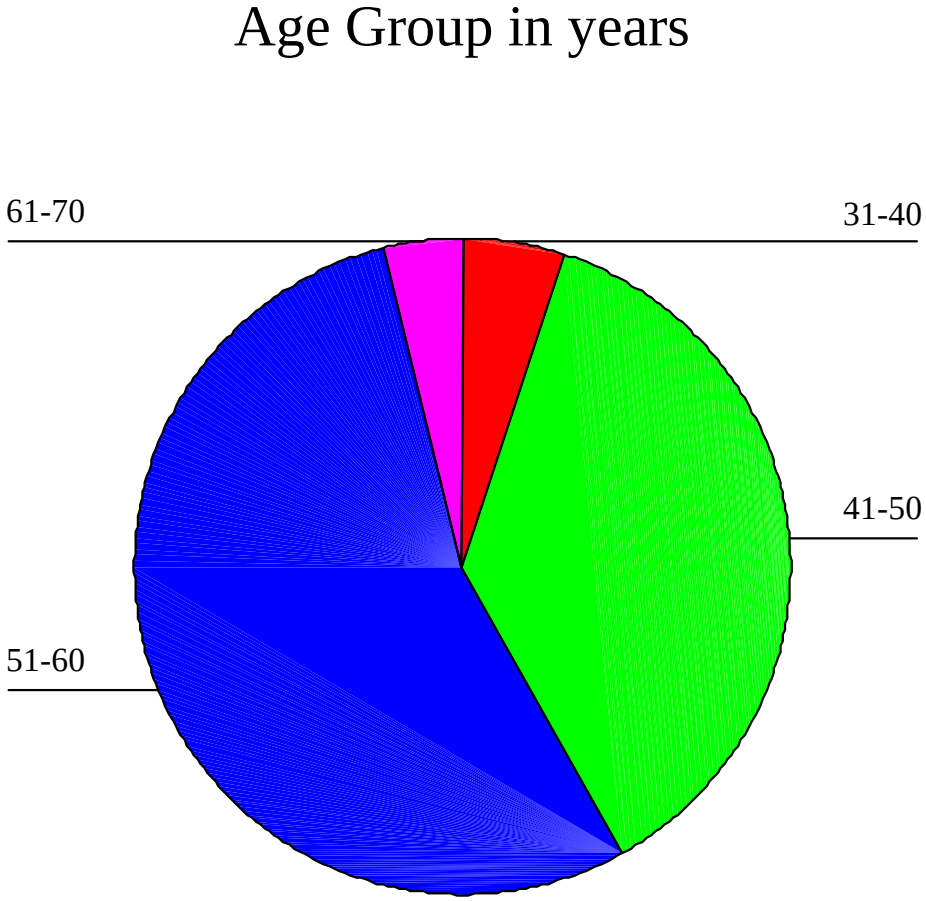
SEX DISTRIBUTION IN CASES

SEX DISTRIBUTION IN CASES	n	%
Male	58	58.0
Female	42	42.0
Total	100	100.0



Age Group in years (CONTROLS)

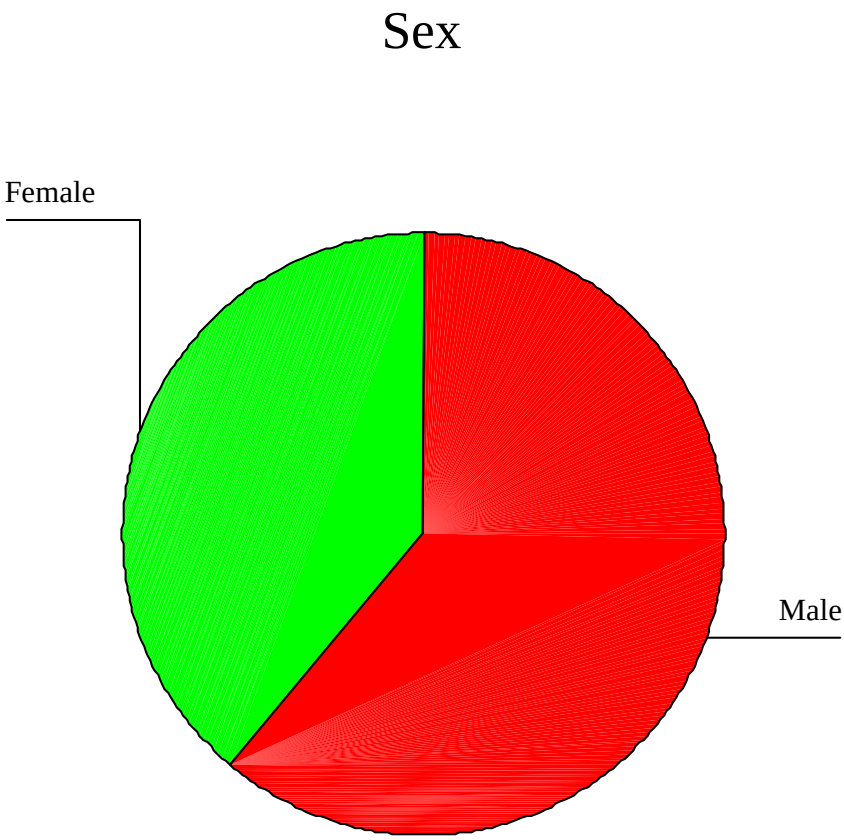
Age Group in years	n	%
31-40	5	5.0
41-50	37	37.0
51-60	54	54.0
61-70	4	4.0
Total	100	100.0



Sex (CONTROLS)

Sex	n	%
Male	61	61.0
Female	39	39.0
Total	100	100.0

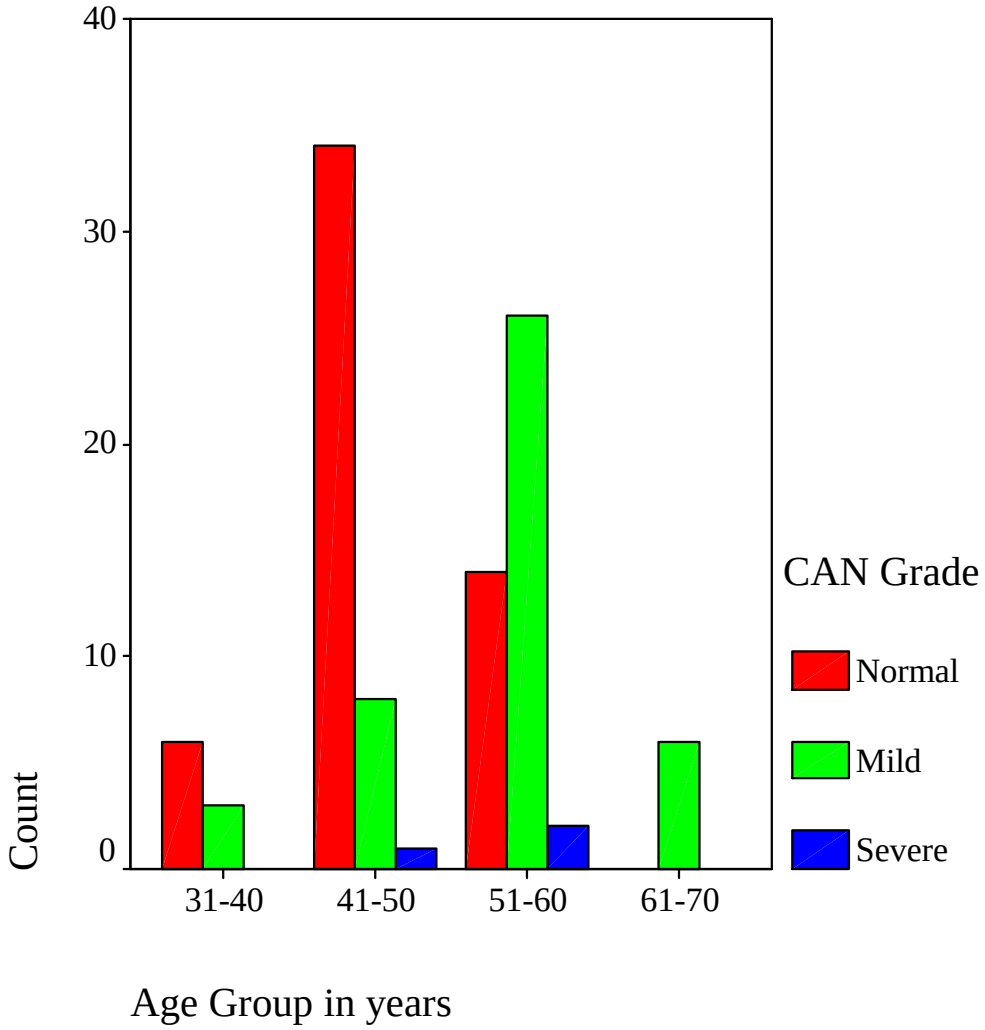
Sex (CONTROLS)



CARDIAC AUTONOMIC NEUROPATHY IN CASES

			CAN Grade			Total	
			Normal	Mild	Severe		
Age Group in years	31-40	Count	6	3	0	9	
		% within Age Group in years	66.7%	33.3%	.0%	100.0%	P value
		% within CAN Grade	11.1%	7.0%	.0%	9.0%	0.000**
	41-50	Count	34	8	1	43	
		% within Age Group in years	79.1%	18.6%	2.3%	100.0%	
		% within CAN Grade	63.0%	18.6%	33.3%	43.0%	
	51-60	Count	14	26	2	42	
		% within Age Group in years	33.3%	61.9%	4.8%	100.0%	
		% within CAN Grade	25.9%	60.5%	66.7%	42.0%	
	61-70	Count	0	6	0	6	
		% within Age Group in years	.0%	100.0%	.0%	100.0%	
		% within CAN Grade	.0%	14.0%	.0%	6.0%	
Total		Count	54	43	3	100	
		% within Age Group in years	54.0%	43.0%	3.0%	100.0%	
		% within CAN Grade	100.0%	100.0%	100.0%	100.0%	

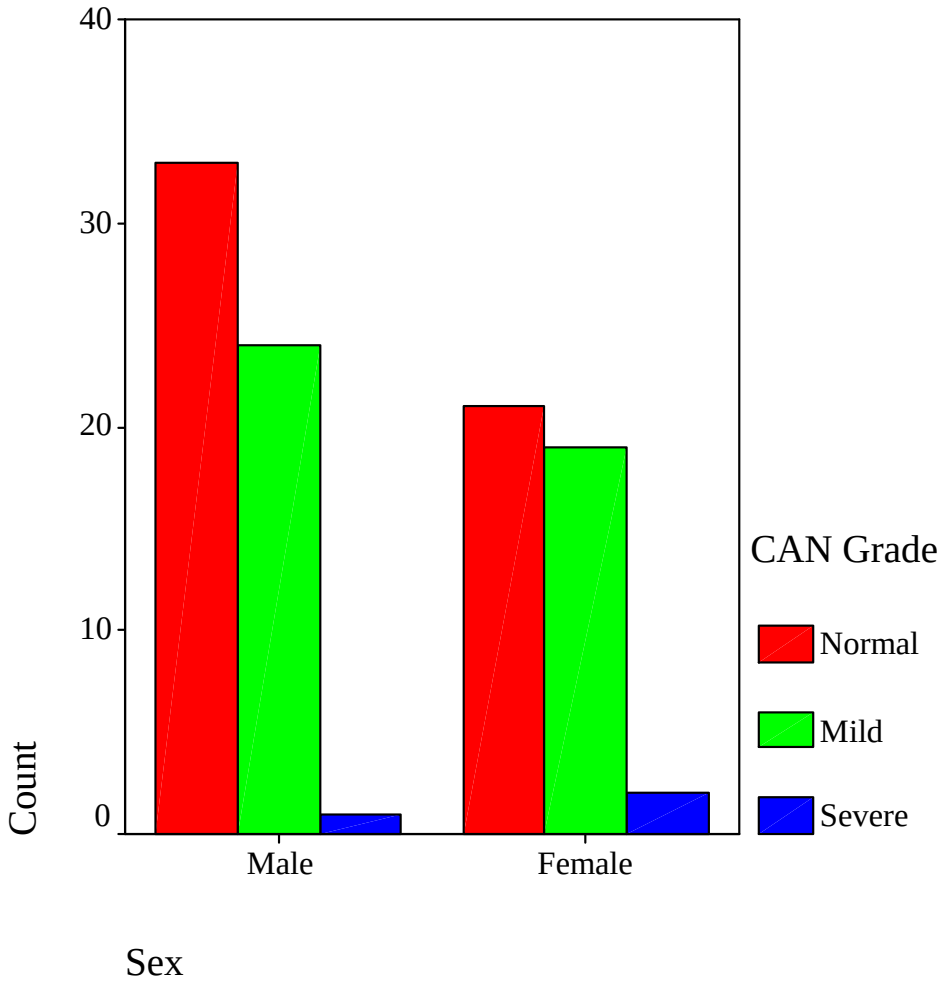
CARDIAC AUTONOMIC NEUROPATHY IN CASES



SEX DISTRIBUTION AND CAN

			CAN Grade			Total
			Normal	Mild	Severe	
Sex	Male	Count	33	24	1	58
		% within Sex	56.9%	41.4%	1.7%	100.0%
		% within CAN Grade	61.1%	55.8%	33.3%	58.0%
	Female	Count	21	19	2	42
		% within Sex	50.0%	45.2%	4.8%	100.0%
		% within CAN Grade	38.9%	44.2%	66.7%	42.0%
Total		Count	54	43	3	100
		% within Sex	54.0%	43.0%	3.0%	100.0%
		% within CAN Grade	100.0%	100.0%	100.0%	100.0%

SEX DISTRIBUTION AND CAN



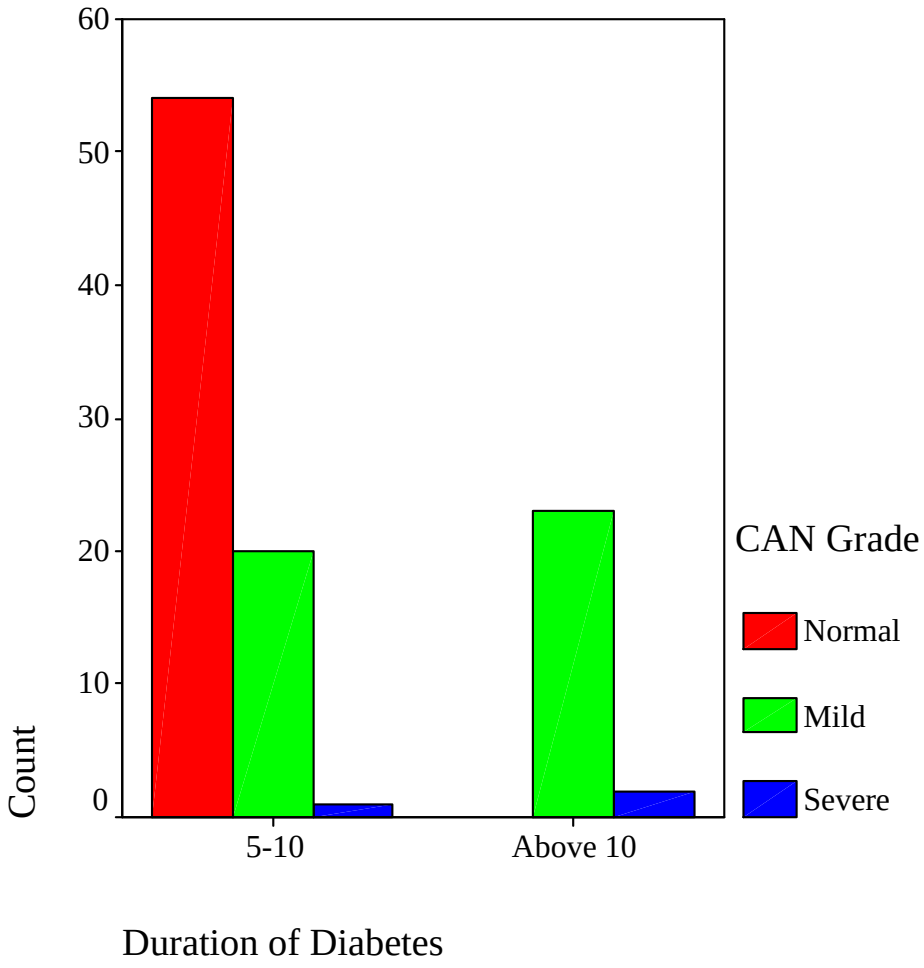
Duration of Diabetes in years

Duration in years	n	%
5-10	75	75.0
Above 10	25	25.0
Total	100	100.0

DURATION OF DIABETES AND CAN

			N Grade			al	
			Normal	Mild	Severe		
Duration of Diabetes	5-10	Count	54	20	1	75	P VALUE 0.000**
		% within Duration of Diabetes	72.0%	26.7%	1.3%	100.0%	
		% within CAN Grade	100.0%	46.5%	33.3%	75.0%	
	Above 10	Count	0	23	2	25	
		% within Duration of Diabetes	.0%	92.0%	8.0%	100.0%	
		% within CAN Grade	.0%	53.5%	66.7%	25.0%	
Total		Count	54	43	3	100	
		% within Duration of Diabetes	54.0%	43.0%	3.0%	100.0%	
		% within CAN Grade	100.0%	100.0%	100.0%	100.0%	

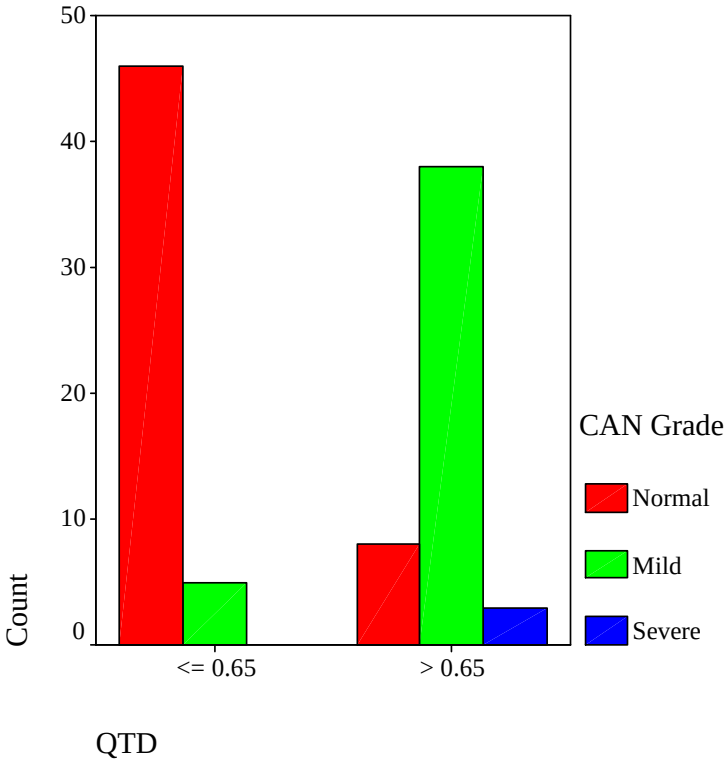
DURATION OF DIABETES AND CAN



QTc DISPERSION IN CASES AND CAN

			CAN Grade			Total	
			Normal	Mild	Severe		
QTD	<= 0.65	Count	46	5	0	51	
		% within QTD	90.2%	9.8%	.0%	100.0%	P VALUE 0.000**
		% within CAN Grade	85.2%	11.6%	.0%	51.0%	
	> 0.65	Count	8	38	3	49	
		% within QTD	16.3%	77.6%	6.1%	100.0%	
		% within CAN Grade	14.8%	88.4%	100.0%	49.0%	
Total		Count	54	43	3	100	
		% within QTD	54.0%	43.0%	3.0%	100.0%	
		% within CAN Grade	100.0%	100.0%	100.0%	100.0%	

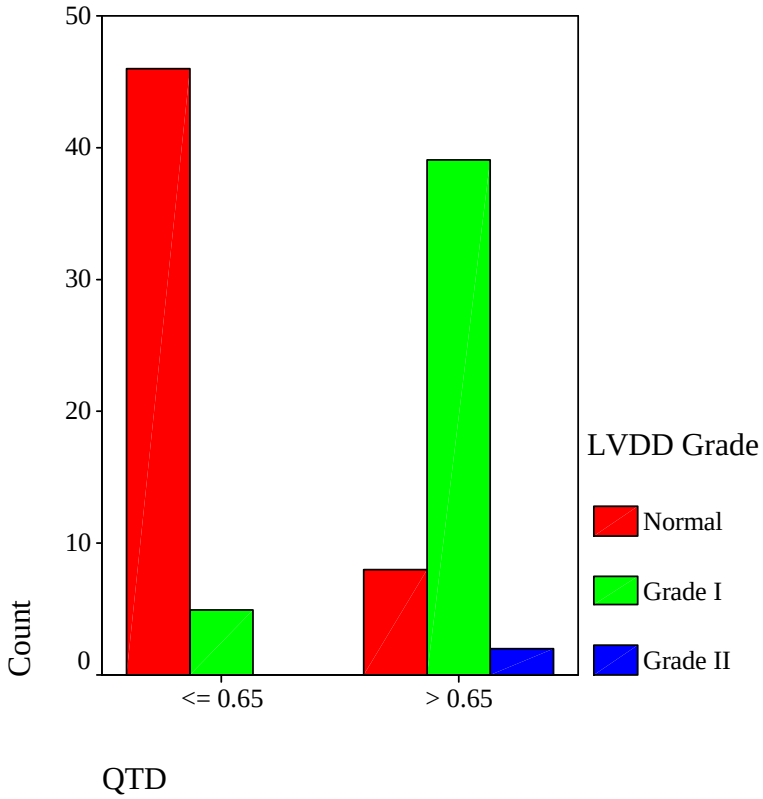
QTc DISPERSION IN CASES AND CAN



QTD AND LVDD

			LVDD Grade			Total	
			Normal	Grade I	Grade II		
QTD	<= 0.65	Count	46	5	0	51	
		% within QTD	90.2%	9.8%	.0%	100.0%	
		% within LVDD Grade	85.2%	11.4%	.0%	51.0%	P VALUE O.OOO**
	> 0.65	Count	8	39	2	49	
		% within QTD	16.3%	79.6%	4.1%	100.0%	
		% within LVDD Grade	14.8%	88.6%	100.0%	49.0%	
Total		Count	54	44	2	100	
		% within QTD	54.0%	44.0%	2.0%	100.0%	
		% within LVDD Grade	100.0%	100.0%	100.0%	100.0%	

QTD AND LVDD



HbA1C AND CAN

	N	Mean	Std. Deviation	
				P VALUE 0.000**
Normal	54	6.815	.2528	
Mild	43	6.279	.6289	
Severe	3	6.767	.0577	
Total	100	6.583	.5221	

BMI AND CAN :

	N	Mean	Std. Deviation	
Normal	54	27.52	2.081	
Mild	43	25.02	3.090	
Severe	3	29.67	1.528	P VALUE 0.000**
Total	100	26.51	2.869	

Concept of P value

If the P value is 0.000 to 0.010 then denoted by ** it imply Significant at 1 level (Highly Significant)

If the P value is 0.011 to 0.050 then denoted by * it imply Significant at 5 level (Significant)

If the P value is 0.051 to 1.000 then do not put star it imply Not Significant at 5 level (Not Significant)

RESULTS

This study consists of 100 type 2 diabetic patients and 100 age and sex matched healthy controls .Among 100 patients 9% between 31-40 years of age 43% between 41-50 years 42% between 51-60 years 6% were between 61-70 years of age. 58% were males . remaining were females ECG ,CAN FUNCTION assessed using analyser , ECHO were done for them . The prevalence of can in study group is high .This study showed significant relation between QTD ,CAN grades and LVDD.

Cardiac autonomic neuropathy more common with longer duration of diabetes. It is associated with obesity and glycemic control. Its incidence increases with age .More common among 50-60 years of age.

Prevalence of diastolic dysfunction assessed by 2D echo is 46 % . It is relatively higher incidence in diabetics than healthy individuals.Its incidence also increases with age and duration of diabetes

There is a significant association with prolongation of QT interval and cardiac autonomic neuropathy . There is association between cardiac autonomic neuropathy and diastolic dysfunction .

DISCUSSION

DISCUSSION

Cardiovascular diseases makes a major list of the complications of diabetes and its mortality .cardiac autonomic neuropathy, ischemic heart disease and diabetic cardiomyopathy are direct complications of diabetes.Risk of heart failure are two to three fold larger in diabetes when compared to non diabetes . DbCM is one of the most common but underevaluated cause of cardiac failure in type 2 diabetes. The pathology of diabetic cardiomyopathy is yet to be explained clearly . In the early stages of the disease diastolic dysfunction is the only abnormality. 2D echo is used to assess diastolic dysfunction.

QT dispersion, that reflects spatial inhomogeneity in ventricular repolarization are associated with increased risk of certain arrhythmias and sudden cardiac death in type 2 diabetic patients and general population.

Several studies, but not all, have found a significantly greater QT dispersion in diabetics Pappachan J M et al studied the utility of prolongation of corrected QT interval (QTc) in the ECG to diagnose CAN in patients with diabetes. They calculated the sensitivity and specificity of QTc prolongation for the diagnosis of CAN were 77% and 62.5% in type 1 and 76.5% and 75% in type 2, respectively.

They concluded that QTc interval in ECG can be used to diagnose CAN with reasonable sensitivity and specificity. This value of sensitivity and specificity correlates with our study.

In another study by jayaprasad et al found association between QTD and cardiac autonomic neuropathy in diabetes . In that study among 50 patients 42% had severe autonomic neuropathy and 24% had early autonomic neuropathy.

Psallas et al conducted a study which showed QTD predict mortality in diabetes and it is associated with worsr prognosis .

Patients in our hospital showed high prevalence of cardiovascular risk factors such as obesity and poor glycemic control.This situation offers a opportunity to study the effect of QTD as a proxy for electrophysiological phenomenon.our study shows the deleterious effect of such risk factors on QTD particularly in long standing diabetes.

In multivariate analysis QTD was predicted by sex, age ,BMI and HbA1C.

As expected patients with diabetes had higher risk of developing QT prolongation than in non diabetics .

In a meta analysis recently concluded that measurementof QTD is a more accurate test for autonomic failure in diabetes. Hyperglycemia causes ventricular instability by increased sympathetic activation.

In our study there is no correlation among sex smoking alcohol with QTD or CAN. In some other study conducted showed significant association of sex and QT prolongation.

C P Mathur et al studied 50 patients with diabetes with 20 normal controls to understand the relationship to CAN with QTc interval. There were 15 (78.94%) cases with QTc prolongation out of 19 diabetics with CAN. None of the diabetics without CAN or control subjects had QTc prolongation. It was observed to have sensitivity o9f 82.6% and specificity of 100%. This value of sensitivity matches the with our study but it does not correlates with specificity value.

CONCLUSIONS

CONCLUSIONS

Prevalence of cardiac autonomic neuropathy is high in long standing diabetics and rises with duration of diabetes. Its incidence is associated poor glycemic control and obesity.

QTC dispersion is significantly high in diabetics with autonomic neuropathy .QTc prolongation and QT dispersion are useful parameters in high risks groups to identify cardiac autonomic neuropathy .It is simple non invasive and cost effective diagnostic tool.By using these tool we can identify subset of people who are at risk of sudden cardic death.

Echocardiography is a standard diagnostic tool in diagnosing DbCM. DbCM is poorly understood complication in longstanding diabetics . It is associated with high morbidity and mortality. Clinical manifestations varies from subclinical ventricular dysfunction to congestive heart failure.

Cardiac autonomic neuropathy correlates with diastolic dysfunction so that we can identify diabetic patients who are more prone to develop DbCM later in sub clinical condition by using simple tool ECG and ECHO .We can decrease morbidity in that

patients by frequent follow up and adequate management.

Cardiac autonomic neuropathy can form the basis for non ischemic diabetic cardiomyopathy . The confirmation of the presence of CAN in otherwise healthy type 2 diabetes patients, and its independent association with resting diastolic dysfunction, is important.

LIMITATIONS OF THE STUDY

LIMITATIONS OF THE STUDY

The study size is small, and hence necessitates the need of a larger study with wide range of study population.

Lack of clinical follow up study . Mortality such as sudden cardiac death cannot be assessed so that we can confirm the influences of autonomic neuropathy Silent ischemia cannot be ruled out by coronary angiogram .More adverse clinical status of patients with CAN makes it difficult to isolate the direct effects of this complication on LV function, even after statistical adjustment. Congenital long QT syndrome cannot be ruled out .

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QTc DISPERSION IN CARDIAC AUTONOMIC NEUROPATHY AND ITS CORRELATION WITH DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES THE BASIS FOR NON ISCHEMIC CARDIOMYOPATHY ?

PROFORMA

Name: Age/Sex:

Address: Occupation:

Op Number**:** BMI :

TYPE 2 DIABETES:

Duration:

Treatment:OHA/INSULIN/MEAL PLAN

PAST HISTORY:

COPD	
CVA	
CKD	
HYPERTENSION	
CAD	
PVD	

PERSONAL HISTORY:

SMOKING

ALCOHOL

GENERAL EXAMINATION:

Pallor

Icterus

Cyanosis

Clubbing

Generalized lymphadenopathy

Pedal edema

VITAL SIGNS:

PR-

BP-

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATIONS:

12 LEAD ECG

2D ECHOCARDIOGRAPHY

Cardiac stress testing if applicable

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Subashini.V.
Post Graduate in M.D. (General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Subashini.V.,

The Institutional Ethics Committee has considered your request and approved your study titled **"QTc DISPERSION IN CARDIAC AUTONOMIC NEUROPATHY AND ITS CORRELATION WITH DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES – THE BASIS FOR NON ISCHEMIC DIABETIC CARDIOMYOPATHY?"**
-
NO.(II) 12032016.

The following members of Ethics Committee were present in the meeting hold on **22.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
5.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Prof.Srinivasagalu,Director,Inst.of Int.Med..MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

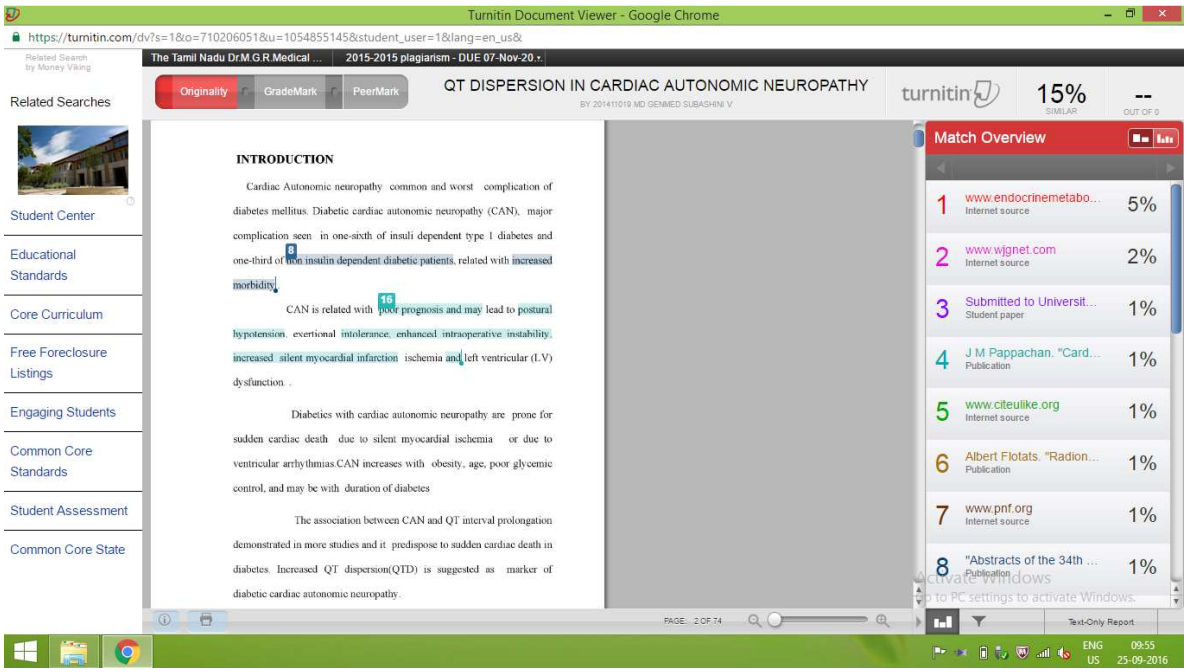
The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

MADRAS MEDICAL COLLEGE
31 MAR 2016
CHENNAI-600 003

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

TURNITIN ANTI PLAGIARISM – CERTIFICATE



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INTRODUCTION

INFORMATION SHEET

We are conducting a study on **"QTc DISPERSION IN CARDIAC AUTONOMIC NEUROPATHY AND ITS CORRELATION WITH DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES THE BASIS FOR NON ISCHEMIC CARDIOMYOPATHY?"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to study the prevalence and risk factors for cardiac autonomic neuropathy (CAN) and the utility of prolongation of corrected QT interval (QTc) in the ECG to diagnose CAN in patients with diabetes mellitus and to identify subset of diabetic patients who are at risk for sudden cardiac death and its correlation with diastolic dysfunction.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator
(V.SUBASHINI)

Signature of Participant

Date :
Place :

PATIENT CONSENT FORM

Study Detail	:	"**QTc DISPERSION IN CARDIAC AUTONOMIC NEUROPATHY AND ITS CORRELATION WITH DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES THE BASIS FOR NON ISCHEMIC CARDIOMYOPATHY?**"
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ❑

Signature/thumb impression	Signature of Investigator
Patient's Name and Address:	Study Investigator's Name: **Dr. SUBASHINI .V.**

MASTER CHART

MASTER CHART

GROUP	SERIALNO	AGE	AGE_G	SEX	DUR_DIA	DIA_G	TREAT	BMI	SMOKER	ALCOHOL	QTD	QTD_G	CAN_GRA	LVDD_GRA	HBA1C	FILTER_$
Cases	1	56	51-60	Female	10	5-10	OHA	29	No	No	0.64	<= 0.65	Mild	Grade I	5.2	0
Cases	2	52	51-60	Male	15	Above 10	OHA	21	No	Yes	0.53	<= 0.65	Mild	Grade I	6.0	0
Cases	3	46	41-50	Female	8	5-10	OHA	27	No	No	0.64	<= 0.65	Normal	Normal	6.5	0
Cases	4	54	51-60	Male	10	5-10	OHA	24	Yes	Yes	0.68	> 0.65	Mild	Grade I	6.5	0
Cases	5	35	31-40	Male	6	5-10	OHA	25	Yes	Yes	0.64	<= 0.65	Mild	Grade I	7.0	0
Cases	6	65	61-70	Female	26	Above 10	OHA	19	No	No	0.68	> 0.65	Mild	Grade I	5.4	0
Cases	7	54	51-60	Female	15	Above 10	OHA	30	No	No	0.67	> 0.65	Severe	Grade I	6.8	0
Cases	8	43	41-50	Male	12	Above 10	OHA	29	No	No	0.58	<= 0.65	Mild	Grade I	6.9	0
Cases	9	54	51-60	Female	20	Above 10	OHA	28	No	No	0.71	> 0.65	Severe	Grade II	6.8	0
Cases	10	45	41-50	Male	10	5-10	OHA	31	Yes	Yes	0.81	> 0.65	Severe	Grade II	6.7	0
Cases	11	64	61-70	Male	20	Above 10	OHA	21	No	No	0.65	<= 0.65	Mild	Grade I	5.1	0
Cases	12	52	51-60	Male	16	Above 10	OHA	24	No	No	0.69	> 0.65	Mild	Grade I	5.6	0
Cases	13	46	41-50	Female	12	Above 10	OHA	29	No	No	0.68	> 0.65	Mild	Grade I	6.8	0
Cases	14	54	51-60	Female	12	Above 10	OHA	26	No	No	0.69	> 0.65	Mild	Grade I	6.7	0
Cases	15	59	51-60	Male	15	Above 10	OHA	29	Yes	Yes	0.78	> 0.65	Mild	Grade I	5.5	0
Cases	16	43	41-50	Female	8	5-10	OHA	29	No	No	0.59	<= 0.65	Normal	Normal	6.9	0
Cases	17	57	51-60	Male	12	Above 10	OHA	21	No	No	0.71	> 0.65	Mild	Grade I	5.3	0
Cases	18	49	41-50	Male	6	5-10	Meal Plan	30	No	Yes	0.56	<= 0.65	Normal	Normal	6.8	0
Cases	19	54	51-60	Male	9	5-10	Meal Plan	28	Yes	Yes	0.74	> 0.65	Mild	Grade I	6.8	0
Cases	20	55	51-60	Male	10	5-10	OHA	29	No	Yes	0.68	> 0.65	Mild	Grade I	6.5	0
Cases	21	58	51-60	Male	12	Above 10	OHA	26	Yes	Yes	0.69	> 0.65	Mild	Grade I	5.5	0
Cases	22	43	41-50	Male	7	5-10	OHA	23	Yes	Yes	0.67	> 0.65	Normal	Normal	6.9	0
Cases	23	44	41-50	Female	6	5-10	OHA	24	No	No	0.69	> 0.65	Normal	Normal	6.8	0
Cases	24	47	41-50	Male	7	5-10	OHA	26	Yes	Yes	0.68	> 0.65	Normal	Normal	7.1	0
Cases	25	56	51-60	Female	12	Above 10	OHA	24	No	No	0.78	> 0.65	Mild	Grade I	5.8	0
Cases	26	49	41-50	Female	6	5-10	OHA	28	No	No	0.65	<= 0.65	Normal	Normal	6.7	0
Cases	27	47	41-50	Male	6	5-10	OHA	29	Yes	Yes	0.64	<= 0.65	Normal	Normal	6.8	0
Cases	28	56	51-60	Female	7	5-10	OHA	24	No	No	0.68	> 0.65	Normal	Normal	5.5	0
Cases	29	54	51-60	Male	12	Above 10	OHA	27	Yes	Yes	0.74	> 0.65	Mild	Grade I	5.9	0
Cases	30	58	51-60	Female	15	Above 10	OHA	21	No	No	0.69	> 0.65	Mild	Grade I	5.4	0
Cases	31	52	51-60	Female	13	Above 10	OHA	23	No	No	0.69	> 0.65	Mild	Grade I	5.9	0
Cases	32	55	51-60	Female	14	Above 10	OHA	23	No	No	0.78	> 0.65	Mild	Grade I	6.8	0
Cases	33	46	41-50	Female	7	5-10	OHA	27	No	No	0.74	> 0.65	Mild	Grade I	6.9	0

Cases	34	43	41-50	Male	7	5-10	OHA	29	No	No	0.60	<= 0.65	Normal	Normal	6.8	0
Cases	35	42	41-50	Male	6	5-10	OHA	27	No	No	0.65	<= 0.65	Normal	Normal	6.8	0
Cases	36	56	51-60	Male	12	Above 10	OHA	24	Yes	Yes	0.67	> 0.65	Mild	Grade I	7.1	0
Cases	37	45	41-50	Male	6	5-10	OHA	28	No	No	0.68	> 0.65	Normal	Normal	6.8	0
Cases	38	43	41-50	Male	6	5-10	OHA	27	Yes	No	0.69	> 0.65	Normal	Normal	6.8	0
Cases	39	57	51-60	Male	9	5-10	OHA	27	Yes	No	0.67	> 0.65	Mild	Grade I	6.9	0
Cases	40	58	51-60	Male	10	5-10	OHA	23	Yes	No	0.69	> 0.65	Mild	Grade I	5.5	0
Cases	41	43	41-50	Female	6	5-10	OHA	29	No	No	0.65	<= 0.65	Normal	Normal	6.9	0
Cases	42	52	51-60	Female	6	5-10	OHA	30	No	No	0.65	<= 0.65	Normal	Normal	6.7	0
Cases	43	44	41-50	Female	6	5-10	OHA	29	No	No	0.67	> 0.65	Normal	Normal	6.9	0
Cases	44	64	61-70	Female	20	Above 10	OHA	23	No	No	0.69	> 0.65	Mild	Grade I	5.5	0
Cases	45	53	51-60	Female	9	5-10	OHA	27	No	No	0.69	> 0.65	Mild	Grade I	5.9	0
Cases	46	63	61-70	Female	20	Above 10	OHA	21	No	No	0.68	> 0.65	Mild	Grade I	5.9	0
Cases	47	45	41-50	Male	6	5-10	OHA	29	Yes	No	0.65	<= 0.65	Normal	Normal	6.9	0
Cases	48	34	31-40	Male	6	5-10	Meal Plan	30	No	No	0.64	<= 0.65	Normal	Normal	7.1	0
Cases	49	45	41-50	Male	7	5-10	OHA	29	Yes	No	0.63	<= 0.65	Normal	Normal	7.1	0
Cases	50	45	41-50	Male	9	5-10	OHA	29	Yes	No	0.67	> 0.65	Mild	Grade I	6.8	0
Cases	51	55	51-60	Male	7	5-10	OHA	28	No	No	0.63	<= 0.65	Normal	Normal	6.5	0
Cases	52	56	51-60	Male	8	5-10	OHA	25	No	No	0.62	<= 0.65	Normal	Normal	6.8	0
Cases	53	57	51-60	Male	7	5-10	OHA	26	Yes	No	0.61	<= 0.65	Normal	Normal	6.9	0
Cases	54	38	31-40	Male	6	5-10	Meal Plan	30	Yes	No	0.61	<= 0.65	Normal	Normal	7.2	0
Cases	55	54	51-60	Male	7	5-10	OHA	28	Yes	No	0.61	<= 0.65	Normal	Normal	6.8	0
Cases	56	57	51-60	Male	7	5-10	OHA	26	Yes	No	0.62	<= 0.65	Normal	Normal	6.9	0
Cases	57	55	51-60	Male	6	5-10	OHA	27	Yes	No	0.68	> 0.65	Mild	Grade I	6.8	0
Cases	58	54	51-60	Male	7	5-10	OHA	26	Yes	No	0.62	<= 0.65	Normal	Normal	6.4	0
Cases	59	49	41-50	Male	6	5-10	OHA	30	Yes	No	0.61	<= 0.65	Normal	Normal	6.9	0
Cases	60	40	31-40	Male	7	5-10	OHA	28	Yes	No	0.62	<= 0.65	Normal	Normal	7.1	0
Cases	61	44	41-50	Female	8	5-10	OHA	23	No	No	0.69	> 0.65	Mild	Grade I	5.8	0
Cases	62	38	31-40	Male	6	5-10	Meal Plan	30	No	No	0.54	<= 0.65	Normal	Normal	6.8	0
Cases	63	45	41-50	Female	7	5-10	OHA	28	No	No	0.52	<= 0.65	Normal	Normal	6.5	0
Cases	64	46	41-50	Male	7	5-10	OHA	23	No	No	0.53	<= 0.65	Normal	Normal	6.9	0
Cases	65	53	51-60	Female	8	5-10	OHA	27	No	No	0.52	<= 0.65	Normal	Normal	6.4	0
Cases	66	55	51-60	Female	7	5-10	OHA	28	No	No	0.59	<= 0.65	Normal	Normal	6.9	0
Cases	67	48	41-50	Female	6	5-10	OHA	27	No	No	0.59	<= 0.65	Normal	Normal	6.8	0
Cases	68	42	41-50	Male	6	5-10	OHA	29	No	No	0.59	<= 0.65	Normal	Normal	6.9	0
Cases	69	59	51-60	Male	8	5-10	OHA	23	No	No	0.61	<= 0.65	Normal	Normal	6.8	0

Cases	70	52	51-60	Female	7	5-10	OHA	28	No	No	0.62	<= 0.65	Normal	Normal	6.4	0
Cases	71	43	41-50	Female	7	5-10	OHA	29	No	No	0.64	<= 0.65	Normal	Normal	6.8	0
Cases	72	34	31-40	Female	6	5-10	Meal Plan	29	No	No	0.62	<= 0.65	Normal	Normal	6.8	0
Cases	73	45	41-50	Female	7	5-10	OHA	28	No	No	0.64	<= 0.65	Normal	Normal	6.9	0
Cases	74	47	41-50	Male	8	5-10	OHA	30	Yes	No	0.62	<= 0.65	Normal	Normal	6.9	0
Cases	75	54	51-60	Male	8	5-10	OHA	23	Yes	No	0.64	<= 0.65	Normal	Normal	6.8	0
Cases	76	54	51-60	Male	8	5-10	OHA	23	Yes	Yes	0.67	> 0.65	Normal	Normal	6.9	0
Cases	77	55	51-60	Male	9	5-10	OHA	21	Yes	No	0.69	> 0.65	Mild	Grade I	6.8	0
Cases	78	43	41-50	Male	6	5-10	OHA	29	Yes	Yes	0.62	<= 0.65	Normal	Normal	7.1	0
Cases	79	38	31-40	Male	6	5-10	Meal Plan	27	Yes	No	0.59	<= 0.65	Normal	Normal	6.9	0
Cases	80	46	41-50	Male	7	5-10	OHA	27	Yes	No	0.58	<= 0.65	Normal	Normal	6.9	0
Cases	81	67	61-70	Male	20	Above 10	OHA	21	Yes	No	0.69	> 0.65	Mild	Grade I	5.8	0
Cases	82	65	61-70	Male	13	Above 10	OHA	22	Yes	No	0.71	> 0.65	Mild	Grade I	5.8	0
Cases	83	48	41-50	Female	6	5-10	OHA	28	No	No	0.64	<= 0.65	Normal	Normal	6.9	0
Cases	84	39	31-40	Female	6	5-10	Meal Plan	29	No	No	0.69	> 0.65	Mild	Grade I	7.1	0
Cases	85	40	31-40	Female	6	5-10	OHA	27	No	No	0.75	> 0.65	Mild	Grade I	6.8	0
Cases	86	41	41-50	Female	6	5-10	OHA	29	No	No	0.71	> 0.65	Mild	Grade I	6.9	0
Cases	87	42	41-50	Female	7	5-10	OHA	28	No	No	0.75	> 0.65	Mild	Grade I	6.8	0
Cases	88	46	41-50	Female	6	5-10	OHA	30	No	No	0.64	<= 0.65	Normal	Normal	6.9	0
Cases	89	56	51-60	Female	8	5-10	OHA	28	No	No	0.71	> 0.65	Mild	Grade I	6.7	0
Cases	90	47	41-50	Male	6	5-10	OHA	28	No	No	0.61	<= 0.65	Normal	Normal	7.1	0
Cases	91	48	41-50	Male	7	5-10	OHA	29	No	No	0.64	<= 0.65	Normal	Normal	7.0	0
Cases	92	57	51-60	Male	15	Above 10	OHA	23	Yes	No	0.69	> 0.65	Mild	Grade I	6.9	0
Cases	93	58	51-60	Male	12	Above 10	OHA	22	Yes	No	0.69	> 0.65	Mild	Grade I	6.5	0
Cases	94	49	41-50	Male	7	5-10	OHA	29	Yes	No	0.71	> 0.65	Mild	Grade I	6.8	0
Cases	95	59	51-60	Male	12	Above 10	OHA	22	Yes	No	0.71	> 0.65	Mild	Grade I	6.7	0
Cases	96	45	41-50	Male	6	5-10	OHA	28	Yes	No	0.64	<= 0.65	Normal	Normal	6.9	0
Cases	97	48	41-50	Female	6	5-10	OHA	25	No	No	0.62	<= 0.65	Normal	Normal	6.8	0
Cases	98	48	41-50	Female	6	5-10	OHA	28	No	No	0.64	<= 0.65	Normal	Normal	6.8	0
Cases	99	45	41-50	Female	7	5-10	OHA	28	No	No	0.63	<= 0.65	Normal	Normal	6.9	0
Cases	100	55	51-60	Female	8	5-10	OHA	26	No	No	0.69	> 0.65	Mild	Grade I	6.7	0
Control	1	46	41-50	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	2	45	41-50	Female	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	3	54	51-60	Male	.	.	.	.	.	.	0.28	<= 0.65	Normal	.	.	1
Control	4	39	31-40	Male	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	5	45	41-50	Male	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1

Control	6	43	41-50	Female	.	.	.	.	.	.	0.65	<= 0.65	Normal	.	.	1
Control	7	34	31-40	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	8	54	51-60	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	9	57	51-60	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	10	54	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	11	43	41-50	Male	.	.	.	.	.	.	0.28	<= 0.65	Normal	.	.	1
Control	12	45	41-50	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	13	46	41-50	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	14	45	41-50	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	15	39	31-40	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	16	56	51-60	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	17	57	51-60	Female	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	18	45	41-50	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	19	59	51-60	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	20	45	41-50	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	21	56	51-60	Female	.	.	.	.	.	.	0.28	<= 0.65	Normal	.	.	1
Control	22	45	41-50	Female	.	.	.	.	.	.	0.27	<= 0.65	Normal	.	.	1
Control	23	53	51-60	Female	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	24	39	31-40	Female	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	25	54	51-60	Female	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	26	45	41-50	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	27	46	41-50	Male	.	.	.	.	.	.	0.29	<= 0.65	Normal	.	.	1
Control	28	49	41-50	Male	.	.	.	.	.	.	0.31	<= 0.65	Normal	.	.	1
Control	29	43	41-50	Male	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	30	42	41-50	Male	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	31	57	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	32	54	51-60	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	33	53	51-60	Male	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	34	57	51-60	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	35	45	41-50	Female	.	.	.	.	.	.	0.33	<= 0.65	Normal	.	.	1
Control	36	44	41-50	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	37	43	41-50	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	38	46	41-50	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	39	67	61-70	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	40	67	61-70	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	41	52	51-60	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1

Control	42	43	41-50	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	43	54	51-60	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	44	56	51-60	Male	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	45	44	41-50	Female	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	46	43	41-50	Female	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	47	45	41-50	Male	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	48	54	51-60	Male	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	49	56	51-60	Female	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	50	55	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	51	57	51-60	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	52	67	61-70	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	53	52	51-60	Male	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	54	45	41-50	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	55	48	41-50	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	56	47	41-50	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	57	54	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	58	67	61-70	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	59	57	51-60	Female	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	60	59	51-60	Male	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	61	45	41-50	Male	.	.	.	.	.	.	0.32	<= 0.65	Normal	.	.	1
Control	62	58	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	63	57	51-60	Male	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	64	45	41-50	Male	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	65	36	31-40	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	66	45	41-50	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	67	54	51-60	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	68	56	51-60	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	69	54	51-60	Male	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	70	56	51-60	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	71	60	51-60	Male	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	72	58	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	73	56	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	74	54	51-60	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	75	45	41-50	Female	.	.	.	.	.	.	0.39	<= 0.65	Normal	.	.	1
Control	76	43	41-50	Female	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	77	56	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1

Control	78	45	41-50	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	79	57	51-60	Female	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	80	58	51-60	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	81	46	41-50	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	82	46	41-50	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	83	55	51-60	Female	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	84	57	51-60	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	85	58	51-60	Female	.	.	.	.	.	.	0.34	<= 0.65	Normal	.	.	1
Control	86	57	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	87	56	51-60	Female	.	.	.	.	.	.	0.38	<= 0.65	Normal	.	.	1
Control	88	45	41-50	Male	.	.	.	.	.	.	0.38	<= 0.65	Normal	.	.	1
Control	89	47	41-50	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	90	54	51-60	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	91	53	51-60	Female	.	.	.	.	.	.	0.35	<= 0.65	Normal	.	.	1
Control	92	54	51-60	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	93	57	51-60	Female	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	94	54	51-60	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	95	56	51-60	Male	.	.	.	.	.	.	0.30	<= 0.65	Normal	.	.	1
Control	96	57	51-60	Male	.	.	.	.	.	.	0.39	<= 0.65	Normal	.	.	1
Control	97	56	51-60	Male	.	.	.	.	.	.	0.38	<= 0.65	Normal	.	.	1
Control	98	58	51-60	Male	.	.	.	.	.	.	0.37	<= 0.65	Normal	.	.	1
Control	99	54	51-60	Female	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1
Control	100	56	51-60	Male	.	.	.	.	.	.	0.36	<= 0.65	Normal	.	.	1